On Neuroimaging Correlates of Aggression in Psychoses

Dissertation

For the Attainment of the Academic Degree
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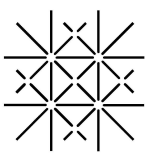

Declaration

I, Sonja Widmayer, declare that this thesis titled "On Neuroimaging Correlates of Aggression in Psychoses" and the work presented in it are my own. I confirm that:

- This work was done while in candidature for a research degree at the University of Basel.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.

Signed:

Date:

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List of Acronyms

BPRS	Brief Psychiatric Rating Scale
BPRS-EC	Brief Psychiatric Rating Scale, Excited Component
fMRI	Functional Magnetic Resonance Imaging
GAF	Global Assessment of Functioning
GM	Grey Matter
GMV	Grey Matter Volume

H	Hemisphere
HC	Healthy Controls
HoV	History of Violence
IVE-7	Impulsiveness-Venturesomeness-Empathy questionnaire
L	Left
LV	Lateral Ventricles
MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
NVS	Persons with Schizophrenia without a History of Violence ("Non-Violent Schizophrenia")
OAS	Overt Aggression Scale
OFC	Orbitofrontal Cortex
PANSS	Positive and Negative Syndrome Scale
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
R	Right
ROI	Region of Interest
sMRI	Structural Magnetic Resonance Imaging
SANS	Scale for the Assessment of Negative Symptoms
SPSS	Statistical Package for Social Sciences
SSD	Schizophrenia-Spectrum Disorders
VBM	Voxel-Based Morphometry
VS	Persons with Schizophrenia with a History of Violence ("Violent Schizophrenia")
WB	Whole Brain

Abstract

Introduction. Aggressive behaviour in persons with a psychotic disorder is clinically highly relevant because of its impact on patients' families, society and caregivers - also, it increases stigmatization of psychiatric patients in general. The neurobiological processes triggering aggression in psychoses are little known. A comprehension of these underlying mechanisms could enhance the predictability and prevention of violent acts and permit a specialized and more individualized patient treatment - also, this could drastically reduce stigmatization. Here, we investigated the neurobiological underpinnings of aggression in psychoses by means of magnetic resonance imaging.

Methods. We performed two systematic reviews examining results on structural and functional magnetic resonance imaging correlates of aggression in persons with psychoses in order to synthesize the current knowledge in this field. Also, we calculated an effect size analysis on structural correlates of aggression in psychoses. Then, we conducted a voxel-based morphometry (VBM) study investigating correlates of an agitated-aggressive syndrome in early psychoses.

Results. We systematically reviewed twelve studies on structural magnetic resonance imaging correlates of aggression in psychoses including a total of 314 patients and 96 healthy control participants (HC). Qualitative analyses showed lower volumes of whole brain (WB), prefrontal regions, temporal lobe, hippocampus, thalamus, and cerebellum, and larger volumes of the lateral ventricles, amygdala and putamen in violent (VS) as opposed to non-violent schizophrenia persons (NVS). In the quantitative effect size analyses, violent persons with schizophrenia exhibited a significantly lower WB volume than HC ($p = 0.004$) and than non-violent persons with schizophrenia ($p = 0.007$).

Our systematic review on functional magnetic resonance imaging correlates of aggression in psychoses included twelve studies with 236 patients and 92 HC. During the n-back tasks, VS as opposed to NVS hypoactivated their inferior parietal lobe. When anticipating shock, VS versus NVS hyperactivated their medial prefrontal gyrus, cuneus, middle temporal gyrus and middle occipital gyrus. When viewing negative emotional pictures, VS versus NVS hyperactivated the middle frontal gyrus, inferior frontal gyrus, anterior cingulate, lingual gyrus, precentral gyrus, globus pallidus, mid-cingulate, and precuneus.

In our study examining VBM correlates in early psychoses we found reduced lingual gyrus volumes in persons with early psychoses with an agitated-aggressive syndrome as opposed to HC.

Conclusion. We found nonsystematic structural and functional correlates of aggression in psychoses. In total, only very little studies on the neurobiological underpinnings of aggression in psychoses have been conducted. There have been no attempts to replicate any of the observed findings in the published literature. Focusing on future directions, we recommend that authors adhere to clear definitions of aggression, measurements of psychopathology, comorbidities and medication. In particular, replication studies would allow for a better synthesis of the findings. Furthermore, there are no studies on affective psychoses or early psychoses. Our pilot study on VBM correlates of aggression in early psychoses provides a first hint towards the hypothesis that the lingual gyrus volume may be inversely correlated with an agitated-aggressive syndrome in early stages of psychoses.

1 Introduction

Aggressive behaviour in persons with a psychotic disorder is clinically highly relevant because of its impact on patients' families, society and caregivers - also, it increases stigmatization of psychiatric patients in general. Still, most persons suffering from psychoses are not violent (Silverstein, Del Pozzo, Roché, Boyle, & Miskimen, 2015) - they are, on the contrary, at an increased risk of becoming victims of violence with risks up to 14 times the rate of being victimized compared with being the perpetrator (Brekke, Prindle, Bae, & Long, 2001). According to Walsh et al. (2002), less than 10% of the violent crimes in society are attributable to schizophrenia.

Yet some individuals with affective and non-affective psychotic disorders are at increased risks for aggressive and violent behaviour (Swanson et al., 2006; Feldmann, 2001; Fazel, Gulati, Linsell, Geddes, & Grann, 2009; Wallace, Mullen, & Burgess, 2004). This is also the case for the first episode of illness (Foley et al., 2005; Large & Nielssen, 2011; Huber et al., 2012; Huber, Hochstrasser, Meister, Schimmelmann, & Lambert, 2016), and there may be an increased agitated-aggressive syndrome in persons with an at-risk mental state (Huber et al., 2014).

However, the nature of the association between psychosis and violence has long been debated. Past research findings are mixed and depend on numerous influential factors. In order to examine the association between violence and psychosis, Fazel et al. (2009) conducted a systematic review and meta-analysis and found substantial heterogeneity between studies reporting risk of violence in patients with psychoses. The authors concluded that schizophrenia and other psychoses are associated with violence and in particular, homicide. However, substance use disorder as comorbidity is a powerful mediator: The risk in schizophrenia patients with substance use disorder comorbidity is similar to that in patients with substance use disorder without psychosis (Fazel, Gulati, Linsell, Geddes, & Grann, 2009).

The neurobiological processes triggering aggression in psychoses are little known. A comprehension of these underlying mechanisms could enhance the predictability and prevention of violent acts and permit a specialized and more individualized patient treatment - also, this could drastically reduce stigmatization. Magnetic resonance imaging (MRI) has often been used to investigate the neurobiological underpinnings of different conditions of the human mind. This method takes a role of fundamental importance in diagnostic medicine and in basic research (Logothetis, 2008). Therefore, using MRI in the quest for a biological understanding of psychological mechanisms and patterns of behaviour is a very promising approach.

In this thesis we aimed at investigating the neurobiological underpinnings of aggression in psychoses by means of MRI. We systematically examined results on structural and functional magnetic resonance imaging correlates of aggression in persons with psychoses in order to synthesize the current knowledge in this field. Then, we performed a structural magnetic resonance imaging study investigating correlates of aggression in very early stages of psychoses. We will show that MRI studies - the way they have been performed up to now - do not yet allow for a deeper understanding of the neurobiological processes underlying aggression in psychoses.

The introduction serves to articulate our research questions and to outline background infor-

mation on structural and functional neuroimaging correlates of aggression in psychotic disorders. Then we summarize the methods and results of our studies and finish by discussing our findings, their impact and their limitations.

1.1 Research Questions

This thesis aimed at identifying structural and functional magnetic resonance imaging correlates of aggression in psychosis, more specifically:

- Are there structural magnetic resonance imaging differences in persons with a psychotic disorder with aggression as opposed to such individuals without aggression?
- Are there functional magnetic resonance imaging differences in persons with a psychotic disorder with aggression as opposed to such individuals without aggression?

To answer these questions, we conducted the following three studies:

- We conducted a systematic review and effect size analysis on structural magnetic resonance imaging correlates of aggression in psychosis. This paper (Widmayer, S., Sowislo, J. F., Jungfer, H. A., Borgwardt, S., Lang, U. E., Stieglitz, R.-D., & Huber, C. G. (2018). Structural Magnetic Resonance Imaging Correlates of Aggression in Psychosis: A Systematic Review and Effect Size Analysis. *Frontiers in Psychiatry, 9.*) is displayed in Appendix A.
- Then, we conducted a systematic review on functional magnetic resonance imaging correlates of aggression in psychosis. This paper (Widmayer, S., Borgwardt, S., Lang, U. E., Stieglitz, R.-D., & Huber, C. G. (2019). Functional Neuroimaging Correlates of Aggression in Psychosis: A Systematic Review with Recommendations for Future Research. *Frontiers in Psychiatry, 9.*) is displayed in Appendix B.
- Last, we performed a study on voxel-based morphometry correlates of aggression in very early psychosis. This paper (Huber, C. G., Widmayer, S., Smieskova, R., Riecher-Rössler, A., Stieglitz, R.-D. & Borgwardt, S. (2018). Voxel-Based Morphometry Correlates of an Agitated-Aggressive Syndrome in the At-Risk Mental State for Psychosis and First Episode Psychosis. *Scientific Reports, 8*(1), 16516.) is displayed in Appendix C.

In the following chapters, we briefly depict background information on structural and functional MRI correlates of psychoses and of aggression.

1.2 Structural Brain Correlates of Psychosis and Aggression

1.2.1 Structural Brain Alterations in Persons with Psychoses

Here, we report findings in affective and non-affective psychoses starting with neuroimaging findings in schizophrenia. Neuroimaging studies indicate that schizophrenia is associated with neuroanatomical abnormalities, with the most replicated findings being ventricular enlargement,

and reductions in frontal and medial temporal lobe grey matter volume (McCarley et al., 1999). Shenton et al. (2001) conducted a review of structural MRI abnormalities in schizophrenia and found 80% of the reviewed studies reporting lateral ventricular enlargement and 73% third ventricle enlargement. All of the reviewed studies discovered that the amygdala, hippocampus, parahippocampal gyrus, and neocortical temporal lobe regions showed decreased volumes in schizophrenia. Wright et al. (2000) conducted a meta-analysis of regional brain volumes in schizophrenia. The authors included 1588 patients with schizophrenia in their analyses. Assuming a volume of 100% in the comparison group, they observed that the mean cerebral volume of the subjects with schizophrenia was smaller (98%), but the mean total ventricular volume of the subjects with schizophrenia was larger (126%). Relative to the cerebral volume differences, the regional volumes of the subjects with schizophrenia were 94% in the left and right amygdala, 94% in the left and 95% in the right hippocampus and amygdala, and 93% in the left and 95% in the right parahippocampus. The largest differences in ventricular subdivisions were in the right and left lateral ventricle, where the volumes of the schizophrenia patients were 116% (Wright et al., 2000). Moreover, an effect size meta-analysis indicated consistent grey matter (GM) reductions in temporal, anterior cingulate, cerebellar, and insular regions associated with onset of a first psychotic episode. GM alterations in the temporal regions were directly related to the severity of psychotic symptoms (Fusar-Poli, Radua, McGuire, & Borgwardt, 2011).

Regarding affective psychoses, Strakowski et al. (1999) detected increased volumes of amygdala, thalamus and globus pallidus in these persons. Altshuler et al. (2000) and Brambilla et al. (2003) confirmed the amygdala volume increase, and Brambilla et al. (2003) found no differences in volumes of the temporal lobe.

In summary, there is clear evidence for structural abnormalities in schizophrenia, in particular an enlargement of the third and fourth ventricles and a volume reduction primarily on the left side of the superior temporal gyrus and frontal brain, mainly in the prefrontal and orbitofrontal regions and parietal lobe (Soyka, 2011).

It has been hypothesized that, on top of the mere effect of illness on brain volume, antipsychotic pharmacotherapy may significantly affect brain structure and account for progressive brain changes during the course of the illness. Two reviews compared studies examining structural MRI in patients taking antipsychotic drugs with antipsychotic-naïve patients and concluded that antipsychotics may contribute to some of the volumetric particularities observed in psychosis (Moncrieff & Leo, 2010; Navari & Dazzan, 2009). Fusar-Poli et al. (2013) conducted a meta-analysis of longitudinal MRI studies to examine the effect of antipsychotics as compared to illness related factors on progressive brain changes in schizophrenia. At baseline, the patients showed significant whole brain volume reductions and enlarged lateral ventricle volumes compared to controls. No baseline volumetric differences were detected in grey matter volumes, white matter volumes, cerebrospinal fluid and caudate nucleus. Longitudinally, there were progressive grey matter volume (GMV) decreases and lateral ventricle (LV) enlargements in patients but not in controls. The GMV decreases were inversely correlated with cumulative exposure to antipsychotic treatments, while no effects were observed for duration of illness or

illness severity. The authors concluded that schizophrenia itself is characterized by progressive grey matter volume decreases and lateral ventricular volume increases, and that some of these neuroanatomical alterations may be associated with antipsychotic treatment. Furthermore, a recently published meta-analysis of studies on patients treated with first- and second-generation antipsychotics revealed a moderating role of medication intake on cortical grey matter (GM) changes: Firstly, more progressive GM loss correlated with higher mean daily antipsychotic intake in patients treated with at least one first-generation antipsychotic. Secondly, less progressive GM loss correlated with higher mean daily antipsychotic intake in patients treated only with second-generation antipsychotics (Vita, De Peri, Deste, Barlati, & Sacchetti, 2015).

1.2.2 Structural Magnetic Resonance Imaging Correlates of Aggression in Healthy Persons

Matthies et al. (2012) obtained morphometric brain scans in 20 healthy volunteers and measured amygdala volumes. All volunteers scored in the normal range of lifetime aggression. Volunteers with higher aggression scores displayed a 16-18% reduction of amygdala volumes. There was a highly significant negative correlation between amygdala volumes and trait aggression. The authors suggested that amygdala volumes might be a marker for the personality property of aggressiveness in healthy human beings. Bufkin and Luttrell (2005) conducted a review of neuroimaging studies on the subject and concluded that the areas associated with aggressive behavioural histories, particularly impulsive acts, are located in the prefrontal cortex and the medial temporal regions. They explained these findings in the context of negative emotion regulation.

1.2.3 Structural Magnetic Resonance Imaging Correlates of Aggression in Patient Populations

Most of the research on structural correlates of aggression has been performed in patient populations with antisocial personality disorder and/or psychopathy. Yang and Raine (2009), in a meta-analysis on the association between structural brain imaging findings and violence found significantly reduced volumes in prefrontal structures in antisocial individuals. Antisocial behaviour was associated with volume reductions in the right orbitofrontal cortex, right anterior cingulate cortex and left dorsolateral prefrontal cortex. In a review by Weber et al. (2008), the authors reported that the literature shows a reduction in prefrontal grey matter volume, grey matter loss in the right superior temporal gyrus, amygdala volume loss, a decrease in posterior hippocampal volume, an exaggerated structural hippocampal asymmetry, and an increase in callosal white matter volume in psychopathic individuals. The authors concluded that psychopathy seems to be associated with brain particularities in a prefronto-temporo-limbic circuit – regions that are involved in emotional and learning processes. Wahlund and Kristiansson (2009) conducted a review on the subject and encountered eleven structural studies on the brain volume differences in violent individuals. The authors observed differences in the frontal lobes,

the temporal lobes, corpus callosum and amygdala in antisocial and psychopathic individuals compared to healthy controls. However, these studies have come to different conclusions: some showed smaller volumes in temporal lobes in violent patients, some in frontal brain areas. Other studies found no volumetric differences between psychopathic persons or subjects with antisocial personality disorder compared to healthy controls. Raine et al. (2003) compared the corpus callosum in subjects with antisocial personality disorder and high degree of psychopathy with healthy controls. They found an increased callosal white matter volume, increase in length, and reduction in callosal thickness in the psychopathic individuals compared to the controls. Summing up, findings about structural correlates of aggression in persons with antisocial personality disorder and/or psychopathy suggest a reduction in prefrontal and temporal volume as compared to healthy controls.

1.3 Functional Brain Correlates of Psychosis and Aggression

1.3.1 Functional Magnetic Resonance Imaging in Persons with Psychoses

Particularities in brain functioning as measured by fMRI have been found in schizophrenia patients during various neuropsychological tests. Here, we focus on working memory and emotion induction and recognition tasks, because they have been examined in the context of aggression in psychoses. Schizophrenia patients as opposed to healthy controls showed deficient working memory performance with significantly larger left dorsolateral prefrontal cortex activation and increased spacial heterogeneity of this activation - also, only persons with schizophrenia activated the basal ganglia and the thalamus during working memory (Manoach et al., 2000). Jansma et al. (2004) found hyperactivations in schizophrenia as opposed to HC during working memory performance in the dorsolateral PFC, the inferior parietal cortex bilaterally and the anterior cingulate. With respect to face affect recognition in persons with psychoses, there are inconsistent reports. Kosaka et al. (2002) found that both persons with psychoses as well as healthy controls activate the amygdala when viewing emotional faces. Habel et al. (2010), on the contrary, reported dysfunctions in the AC, bilateral dorsomedial PFC, the right superior temporal gyrus and the right fusiform gyrus in persons with psychoses as opposed to HC. Gur et al. (2002) stated that persons with psychoses hypoactivated limbic regions when viewing emotional faces. A meta-analysis showed that persons with psychoses hypoactivated the bilateral amygdala, visual processing areas, anterior cingulate cortex, dorsolateral frontal cortex, medial frontal cortex and subcortical structures. Persons with psychoses hyperactivated the cuneus, parietal lobule, precentral gyrus, and superior temporal gyrus (Taylor et al., 2012).

1.3.2 Functional Correlates of Aggression in Healthy Persons

Lotze et al. (2007) examined social reactive aggression in healthy participants by means of fMRI. The authors used a competitive reaction time task to investigate brain regions involved in social interaction and reactive aggression in sixteen healthy male participants. They were provoked by increasingly aversive stimuli and were given the opportunity to respond aggressively against

their opponent by administering a stimulus as retaliation. fMRI revealed an increase of medial prefrontal cortex activation during retaliation. The dorsal medial prefrontal cortex (mPFC) was active when participants had to select the intensity of the retaliation stimulus, and its activity correlated with the selected stimulus strength. In contrast, ventral mPFC was active during observing the opponent suffering but also during retaliation independent of stimulus strength. Ventral mPFC activation, stronger in low callous subjects, correlated positively with skin conductance response during observation of the suffering opponent. The authors concluded that dorsal mPFC activation seems to represent cognitive operations related to more intense social interaction processes whereas the ventral mPFC might be involved in affective processes associated with compassion to the suffering component.

Siever (2008), in a review, observed that an important abnormality implicated in aggression is hyperactivity of the limbic system in response to negative or provocative stimuli, particularly anger provoking stimuli.

1.3.3 Functional Magnetic Resonance Imaging Correlates of Aggression in Patient Populations

Coccaro et al. (2007) examined brain activity in individuals with impulsive aggression. In their study, persons with impulsive aggression and healthy controls underwent functional MRI while viewing blocks of emotionally salient faces. The authors compared amygdala and orbitofrontal cortex (OFC) reactivity to faces between the two groups and found that relative to controls, patients exhibited higher amygdala reactivity and lower orbitofrontral cortex activation to faces expressing anger. Furthermore, the extent of amygdala and OFC activation to angry faces were differentially related to previous aggressive behaviour of the participants. While healthy controls did, aggressive subjects did not demonstrate amygdala-OFC coupling during responses to angry faces. The authors conclude that these findings indicate an amygdala-OFC dysfunction in response to a social threat signal (processing angry faces) in individuals with a history of impulsive aggressive behavior. Furthermore, the authors suggest their findings to substantiate a link between a dysfunctional cortico-limbic network and aggression. New et al. (2007) provoked aggression in a laboratory setting with the Point Subtraction Aggression Paradigm. Patients with borderline personality disorder with an anger dyscontrol, as opposed to HC, showed hypoactivations to provocation in the medial frontal cortex and the anterior frontal cortex but hyperactivations in the orbital frontal cortex (New et al., 2007). According to a review by Siever (2008), an imbalance between prefrontal regulation and hyperactivation of the amygdala and other limbic regions plays an important role for aggression in different patient populations.

In the next chapters we describe methods and results of our studies.

2 Systematic Reviews and Effect Size Analysis

We conducted two systematic reviews: one on structural and one on functional magnetic resonance imaging correlates of aggression in psychoses.

2.1 Methods

The corresponding papers detailing in full our study protocols, results and discussions can be found in Appendices A and B.

2.1.1 Search and Selection Strategy

We conducted two systematic reviews, one including an effect size analysis, searching EMBASE, ScienceDirect, and PsycINFO through September 2017. We used search thesauri representing aggression, psychosis and structural or functional brain imaging, respectively. We searched the reference lists of the selected original articles for additional literature and screened all studies according to the following inclusion criteria. We included longitudinal, cross-sectional, and case-control studies (journal articles, book chapters, and dissertations) reporting brain imaging correlates of aggression comparing:

- affective or non-affective psychosis groups with a history of violence, or including continuous measures of aggression,
- affective or non-affective psychosis groups with a history of violence or including continuous measures of aggression compared with healthy controls,
- affective or non-affective psychosis groups with a history of violence or including continuous measures of aggression compared to controls with diagnoses other than affective or non-affective psychoses,
- affective or non-affective psychosis groups with a history of violence compared to affective or non-affective psychosis groups without a history of violence.

Furthermore, we included only brain imaging studies examining cases and controls with an age of at least 18 years. We applied no language restriction and required patients to have an established diagnosis of affective or non-affective psychosis according to DSM or ICD.

2.1.2 Quality Assessments

To achieve a high standard of reporting we adopted the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) guidelines (Moher et al., 2009) and the revised "Quality of Reporting of Meta-Analyses" (QUORUM) statements (Moher et al., 1999). The detailed search protocols are available on the International Prospective Register of Systematic Reviews (PROSPERO) as follows:

- structural systematic review and effect size analysis: PROSPERO registration number: CRD42014014461
- functional systematic review: PROSPERO registration number: CRD42016048579

For both systematic reviews, we assessed methodological quality using the PRISMA checklist (Moher et al., 2009).

2.1.3 Data Extraction

Main outcome measures of the structural systematic review were the whole brain volumes of the two patient groups (VS and NVS) and of the HC group. For the functional review, hyper- and hypoactivations in these groups were the main outome measures. For more detailed information, please see Appendices A and B.

For both reviews, we extracted the following information from all studies: imaging center, first author, year of publication, type of imaging analysis, population characteristics of all groups, operationalization of aggression and diagnosis.

2.1.4 Data Analysis

The qualitative analyses of all included publications for both reviews are detailed in Appendices A and B.

2.1.4.1 Review on Structural MRI Correlates of Aggression in Psychoses

We performed a one-way ANOVA to describe group characteristics. We calculated effect sizes separately for each study and effect sizes of global brain volumes. All analyses were performed with "Statistical Package for Social Sciences" (SPSS). For meta-analytic calculations we used the SPSS macros written by Lipsey and Wilson (2001). We calculated the pooled standard deviation, then standardized the mean effect size from statistical information reported in the studies. We corrected for the bias of small sample sizes (less than 20 subjects) using Hedge's method in order to receive an unbiased effect size estimate. We then calculated the effect size for each study separately using the unbiased effect size estimate. Finally, we weighted the effect size depending on each group's sample size.

2.1.4.2 Review on Functional MRI Correlates of Aggression in Psychoses

We transformed Talairach coordinates into MNI coordinates using GingerALE (`http://www.-brainmap.org/software.html`). To provide an overview on hyper- and hypoactivation patterns, we produced multislice activation pattern figures in MRIcron (`https://www.nitrc.org/projects/-mricron`) using the reported MNI coordinates for building threedimensional ROIs.

2.2 Results

2.2.1 Structural Magnetic Resonance Imaging Correlates of Aggression in Psychoses: A Systematic Review and Effect Size Analysis

Our sample consisted of twelve studies with a total of 470 patients and 155 HC. Considering subject overlaps due to the publication of multiple papers using the same cohort, the sample consisted of 314 patients and 96 HC.

Appendix A shows the detailed study selection procedure as a PRISMA flow diagram. It also gives an overview of all included studies showing imaging center, name of the first author, year of publication, type of imaging analysis, population characteristics of HC, patient groups (group size, gender, age, psychopathology, IQ, medication) and diagnosis.

Table 1: Descripitive statistics over the twelve structural MRI studies included

	HC *M(SD)*	NVS *M(SD)*	VS *M(SD)*	Group differences (ANOVA) *p*
Sample Size	24.0 (6.9)	20.4 (4.9)	24.4 (9.3)	0.568
Average % male	72.9 (41.4)	79.6 (30.0)	82.5 (31.1)	0.898
Age	31.7 (1.2)	36.7 (4.1)	37.6 (3.1)	0.033
IQ	102.9 (2.0)	88.0 (1.9)	84.9 (0.1)	0.003 *

Note. Descriptive statistics of healthy control group (HC), non-violent schizophrenia patients (NVS) and violent schizophrenia patients (VS) over all twelve included studies with exclusion of overlapping cohorts. HC = healthy control group, NVS = non-violent schizophrenia patients, VS = violent schizophrenia patients, M = mean, SD = standard deviation. * The group comparisons VS vs. HC and NVS vs. HC showed significant group differences in IQ (F (2,3) = 73.119) while the groups VS vs. NVS did not differ significantly in IQ.

Among the included studies, there were no significant group differences in sample sizes, age or gender (see Table 1). Regarding WAIS IQ we found significant differences between HC and NVS as well as VS. NVS and VS did not significantly differ in IQ (see Table 1). Missing data impeded calculation of differences regarding antipsychotic medication or psychopathology.

2.2.1.1 Aggression Operationalized as "History of Violence"

Barkataki et al. (2006), Kumari et al. (2009), Kumari et al. (2013), Kumari et al. (2014), Narayan et al. (2007), Yang et al. (2010) and Puri et al. (2008) used the following three groups to examine aggression in psychoses:

- Healthy, non-violent control participants (HC)
- Non-violent persons with schizophrenia (NVS)
- Violent persons with schizophrenia (VS)

Kumari et al. (2009), Kumari et al. (2013), Kumari et al. (2014) and Narayan et al. (2007) published work based on the cohort originally examined by Barkataki et al. (2006).

Most studies found decreased volumes in VS as compared to NVS (Barkataki, Kumari, Das, Taylor, & Sharma, 2006; Kumari et al., 2013; Yang et al., 2010; Puri et al., 2008; Kumari et al., 2009; Narayan et al., 2007; Kuroki et al., 2017), while other studies reported increased volumes in VS (Kumari et al., 2013; Del Bene et al., 2016; Schiffer et al., 2013). Kumari et al. (2014) found no significant differences in brain volumes in VS versus NVS. For an overview, see Figure 1.

Figure 1: Structural Differences in Violent versus Non-Violent Persons with Schizophrenia

Overview of the qualitative findings comparing volumes in violent vs. non-violent schizophrenia patients OR in italic of continuous measures of aggression in schizophrenia patients. WB = Whole Brain, Cer = Cerebellum, TL = Temporal Lobe, I = Insula, LV = Lateral Ventricles, CN = Caudate Nucleus, P = Putamen, T = Thalamus, Hypo = Hypothalamus; Hip = Hippocampus, Am = Amygdala, PFC = Prefrontal Cortex, PMC = Premotor Cortex, SMC = Sensorimotor Cortex, InfP = Inferior Parietal Cortex, OPC = Occipitoparietal Cortex, AC = Anterior Cingulate, OFC = Orbitofrontal Cortex, InfF = Inferior Frontal Cortex, MidF = Middle Frontal Cortex, SupF = Superior Frontal Cortex, PHG = Parahippocampal Gyrus. Articles marked blue used the same cohort, of which the work by Barkataki et al. (2006) was the underlying primary study - The two studies by Hoptman et al. used the same cohort, as well (marked in italic). Red shading refers to relatively decreased volumes in violent schizophrenia versus non-violent schizophrenia patients. Green shading refers to relatively increased volumes in violent schizophrenia versus non-violent schizophrenia patients. Yellow shading refers to no significant differences in volumes between violent schizophrenia versus non-violent schizophrenia patients.

More specifically, Barkataki et al. (2006) found that VS had a significantly reduced whole-brain volume compared to the NVS. The VS group showed significantly larger putamen and smaller amygdala volumes than the NVS group – these findings, though, were not sustained when covarying for PANSS general psychopathology score. Kumari et al. (2013) found that VS had smaller whole brain, temporal lobe and hippocampus volumes than NVS. However, VS had larger amygdala volumes than NVS. When comparing the AC volumes of VS with NVS, there was no significant difference (Kumari et al., 2014). Narayan et al. (2007) found reduced cortical

thickness in the right ventromedial prefrontal and lateral sensorimotor cortex in aggressive versus non-aggressive persons with schizophrenia. Yang et al. (2010) found reduced GM volume in whole brain, hippocampus and parahippocampal gyrus in VS compared with NVS. Puri et al. (2008) detected that VS had smaller GM volumes in the cerebellum than NVS and hypothesized that the cerebellum might be relevant for input from ventrolateral prefrontal cortex and parietal regions.

In the group comparison NVS versus VS we noted large negatively directed effects in whole brain (Barkataki, Kumari, Das, Taylor, & Sharma, 2006), temporal lobe, thalamus, hippocampus, prefrontal cortex, premotor cortex, sensorimotor cortex and occipitoparietal cortex, medium-sized effects in whole brain (Yang et al., 2010) and small effects in OFC and inferior, middle and superior frontal cortex. In the same group comparison, we found large positively directed effects in the amygdala and small effect sizes in LV and putamen.

Results on the other comparisons (HC versus NVS, HC versus VS) are described in Appendix B.

2.2.1.2 Aggression Operationalized by Means of Questionnaires

Hoptman et al. (2005) and Hoptman et al. (2006) used continuous measures to examine structural correlates of violence in schizophrenia in one sample. Hoptman et al. (2005) found larger GM volumes in the left OFC to be associated with a higher degree of aggression as rated in the Positive and Negative Syndrome Scale (PANSS) and Overt Aggression Scale (OAS). Also, larger GM volumes in the right OFC were associated with worse neuropsychological performance. The authors discussed that maybe larger volumes represent reduced neuronal density or other pathophysiological processes. Hoptman et al. (2006) uncovered that aggression in treatment-resistant schizophrenia or schizoaffective disorder is associated with a larger caudate volume. In summary, studies measuring aggression by continuous means (questionnaires) found increased volumes in the OFC as well as the caudate (Hoptman et al., 2005, 2006) (see Figure 1).

2.2.1.3 Effect Size Analysis

After excluding all studies with overlapping cohorts, insufficient data, or missing comparison group, five studies remained. We calculated an effect size analysis over whole brain volumes as reported in the studies by Barkataki et al. (2006), Del Bene et al. (2016), Kuroki et al. (2017), Schiffer et al. (2013) and Yang et al. (2010) (see Table 2).

We observed that HC showed larger whole brain volumes than persons with schizophrenia independently of their history of violence. In addition, studies revealed that VS had smaller whole brain volumes than NVS.

In the next sections, we describe the results of our systematic review on functional MRI correlates of aggression in psychoses.

Table 2: Effect Size Analysis of Whole Brain Volumes

	HC vs NVS				HC vs VS				NVS vs VS			
	n	Mean Effect Size	p	Q	n	Mean Effect Size	p	Q	n	Mean Effect Size	p	Q
WB	4	0.0356	0.8140	1.1197	4	0.4223	0.0042	4.0581	5	0.3555	0.0073	5.2540

Note. Effect size analysis of whole brain volume measured in the studies by Barkataki et al. (2006), Del Bene et al. (2016), Kuroki et al. (2017), Schiffer et al. (2013) and Yang et al. (2010). WB = whole brain, n = number of studies, p = value of probability, Q = Homogeneity Coefficient

2.2.2 Functional Magnetic Resonance Imaging Correlates of Aggression in Psychoses: A Systematic Review

Following the search strategy described on page 7, we found twelve studies on functional MRI correlates of aggression in psychoses including 334 patients and 113 HC. Considering subject overlaps due to the publication of multiple papers using the same cohort, the sample consisted of 236 patients and 92 HC.

Appendix B shows the detailed study selection procedure as a PRISMA flow diagram. It also gives an overview of all included studies showing imaging center, name of the first author, year of publication, type of imaging analysis, population characteristics of HC, patient groups (group size, gender, age, psychopathology, IQ, medication) and diagnosis.

In figure 2, we provide an overview of fMRI activation patterns across all tasks, brain areas and group comparisons.

Here, we only describe the main contrast of interest, namely the comparison VS versus NVS. In working memory, VS as opposed to NVS hypoactivated the right inferior parietal lobe (Kumari et al., 2006). When anticipating shock as induced in the study by Kumari et al. (2009), VS as opposed to NVS hyperactivated their medial prefrontal / cingulate gyrus bilaterally, middle temporal gyrus bilaterally, right posterior cingulate / cuneus and left middle occippital gyrus. In a paradigm with negative emotional pictures, VS as opposed to NVS hyperactivated the right anterior cingulate, right lingual gyrus, left precentral gyrus, right middle frontal gyrus, right inferior frontal gyrus and superior temporal gyrus, globus pallidus bilaterally, right precuneus and right mid-cingulate (Tikàsz et al., 2016). In the same study, the authors showed that when viewing neutral emotional pictures, VS hyperactivated the right middle frontal gyrus, right inferior temporal gyrus, left middle occipital gyrus and left cerebellar tuber. In an affective theory of mind task, VS as compared to NVS hypoactivated the left ventrolateral PFC and left superior temporal sulcus at the temporoparietal junction (Schiffer et al., 2017).

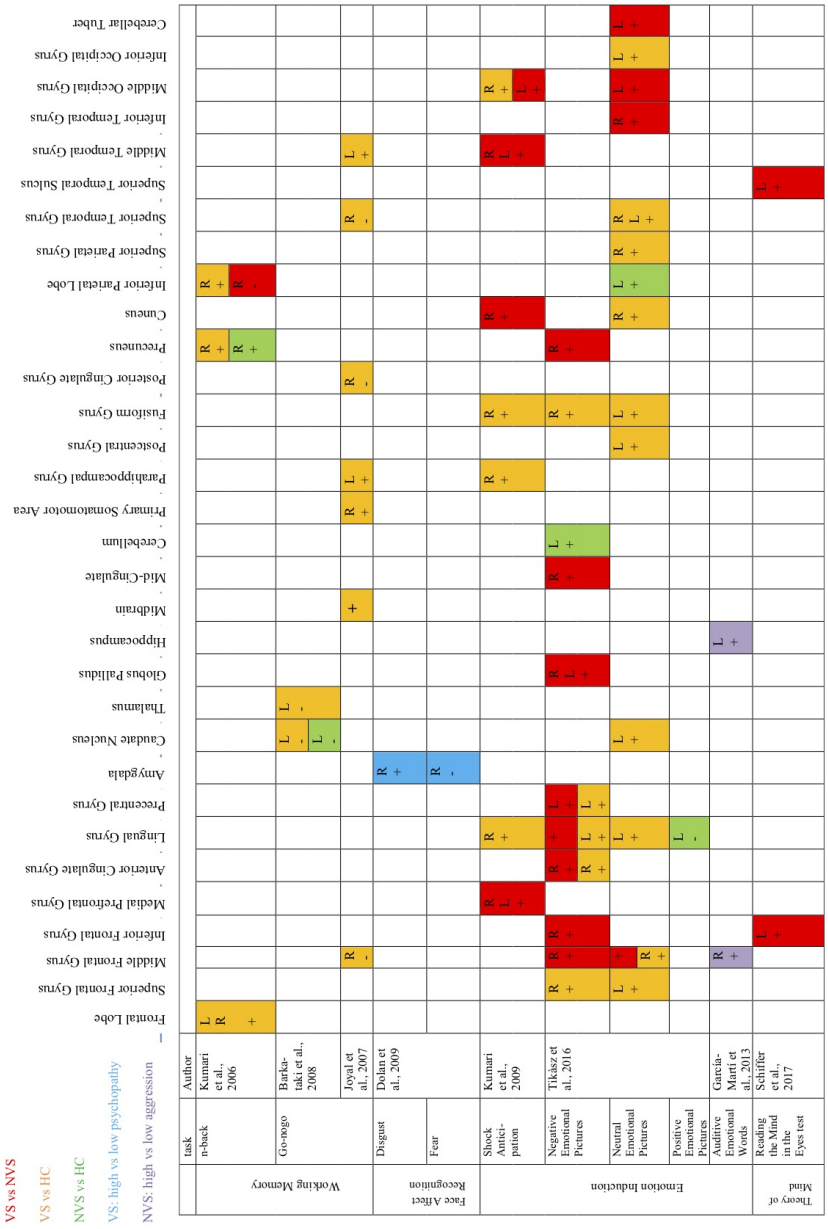

Figure 2: Functional MRI Differences across Tasks and Group Comparisons

fMRI activation patterns across all tasks, brain areas and group comparisons. Hyeractivations are marked with a "+", hypoactivations with a "-". L = left, R = right.

3 Voxel-Based Morphometry Correlates of Aggression in Early Psychosis

In a pilot study on structural MRI correlates of aggession, we examined persons in very early stages of psychosis and with an at-risk mental state.

3.1 Methods

The corresponding paper detailing in full our study protocol, results and discussion can be found in Appendix C.

3.1.1 Study Sample

Our study on sMRI correlates of aggression in early psychoses was performed based on data from the early detection of psychosis project (FePsy) at the Department of Psychiatry, University of Basel, Switzerland (Huber et al., 2014; Riecher-Rössler et al., 2007, 2009). At-risk mental state (ARMS) patients, first episode psychosis (FEP) patients and HC (n = 25) were included. Inclusion criteria for the ARMS group (n = 56) were one or more of the following: a) "attenuated" psychotic symptoms, b) brief intermittent psychotic symptoms, c) a first-degree relative with a psychotic disorder plus a marked decline in social or occupational functioning or d) unspecific risk category (Riecher-Rössler et al., 2007, 2009; Yung, Phillips, Yuen, & McGorry, 2004). FEP patients (n = 55) fulfilled criteria for acute psychotic disorder according to the ICD-10 or DSM-IV. Aggression was operationalized with the BPRS-EC score. We obtained these scores by trained raters during clinical interviews. As an agitated-aggressive syndrome can be already present in ARMS and FEP patients (Huber et al., 2014), we examined FEP and ARMS as one group and dichotomised them according to BPRS-EC scores using a median split ($\text{median}_{\text{BPRS-EC}} = 5$). We then labeled patients with a BPRS-EC score > 5 as the "BPRS-EC high" subgroup (n = 49) and patients with a BPRS-EC score ≤ 5 as the "BPRS-EC low" subgroup (n = 62).

3.1.2 Clinical Assessment Scales

Subjects were assessed with the BPRS, SANS (Andreasen, 1989) and GAF (Spitzer, Gibbon, Williams, & Endicott, 1996). Also, information on current and previous alcohol, nicotine, cannabis and other illegal drug consumption was obtained.

3.1.3 Statistical Analyses of Demographics and Clinical Group Differences

We performed ANOVAs and χ^2-tests to describe group characteristics with regard to gender, age, years of education, BPRS total score and BPRS-EC, SANS total score, GAF score, intake of antipsychotics and antidepressants, as well as consumption of alcohol, cannabis and cigarettes. We then performed post-hoc Bonferroni analyses to identify subgroup differences. Also, we calculated Pearson's correlations for BPRS-EC items and BPRS-EC with BPRS total score, SANS total score, and the BRPS items not included in the BPRS-EC. All analyses were performed with SPSS and $p < 0.05$ was considered significant.

3.1.4 Structural Magnetic Resonance Image Acquisition and Analysis

We acquired a three-dimensional T1-weighted magnetization prepared rapid gradient echo sequence on a 3-T MRI system with sagittal orientation based on a 256 x 256 x 176 matrix with 1 mm isotropic spatial resolution, inversion time (T1) of 1000ms, repetition time (TR) of 2s and echo time (TE) of 3.4ms. We used SPM8 software (`https://www.fil.ion.ucl.ac.uk/spm/software/spm8/`) run in Matlab 7.1 (Math Works, USA) to identify group-related differences in grey matter volume (GMV). Voxel-based morphometry was performed using the VBM8 toolbox (`http://www.neuro.uni-jena.de/vbm/download/`). T1-weighted images were coregistered to the MNI template using a multiple stage affine transformation with 12 estimated parameters of interest. These normalized images were segmented using the "New Segmentation Approach" with different treatment of the mixing proportions. Afterwards the changes in volume were corrected using the DARTEL toolbox (`http://www.neurometrika.org/node/34`) to produce a high-dimensional normalization protocol. We smoothed all preprocessed images using an isotropic 8mm Gaussian kernel.

We performed an analysis of covariance (ANCOVA) to compare grey matter images between our three groups ("BPRS-EC high", "BPRS-EC low" and "HC") in the whole brain using voxel based morphometry. We modelled age, gender and total intracranial volume (ICV) as covariates to reduce the potential impact of these variables on the findings. Statistical significance was assessed at cluster level at a threshold of $p < 0.05$ after family-wise error (FWE) correction. The eigenvariates from between-group contrasts were extracted and used for correlation analyses between grey matter volume by agitated-aggressive syndrome score.

3.2 Results

Demographics and clinical group differences of this study are detailed in Appendix C. Regarding the imaging results, the "BPRS-EC high" group showed significantly lower GMV in the left lingual gyrus as compared to HC. There were no significant between-group differences regarding the contrasts "BPRS-EC high" > HC, "BPRS-EC high" > "BPRS-EC low", "BPRS-EC high" < "BPRS-EC low", patients > HC and patients < HC.

In short, our voxel-based morphometry study showed that individuals in early stages of psychosis with an agitated-aggressive syndrome exhibit significant volumetric reductions in the lingual gyrus as opposed to HC. These volumetric reductions were not evident when comparing BPRS-EC high versus BPRS-EC low groups. This could reflect the significance of disease-related mechanisms already present in early psychoses. Furthermore, treatment with antipsychotic medication may annihilate a potential difference in brain volumes in those early stages of psychoses - there are, to our knowledge, no other studies examining neuroimaging correlates of aggression in early psychoses, which renders it very difficult to interpret our finding of reduced lingual gyrus volume.

4 Discussion

In the following, we discuss the results and implications of our three studies starting with the reviews and effect size analysis, followed up by our voxel-based morphometric correlates of aggression in early psychoses. Also, we outline the limitations of our work. More detailed discussion of our studies can be found in Appendices A, B and C.

4.1 Structural Magnetic Resonance Imaging Correlates of Aggression in Psychoses

Our systematic review on structural magnetic resonance imaging correlates of aggression showed that there are in total few studies that examined this topic. When comparing non-violent as opposed to violent persons with schizophrenia, we found studies reporting volumetric reductions in the whole brain, cerebellum, temporal lobe, caudate nucleus, thalamus, hippocampus, prefrontal cortex, premotor cortex, sensorimotor cortex, and parahippocampal gyrus. The parahippocampal gyrus volume reduction seems to be specific to this group comparison - this structure is known to play an important role in scene recognition (Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999). The ability to recognize scenes is reported to be impaired in violent persons (Kret & de Gelder, 2013) and in persons with schizophrenia (Gold, Poet, Wilk, & Buchanan, 2004).

The putamen, lateral ventricles and amygdala are reported to be larger in VS as opposed to NVS. The putamen volume increase may be an effect of antipsychotic medication, while the amygdala volume is usually reported as being reduced in persons with schizophrenia and in aggressive persons. The amygdala as part of the limbic system plays an important role in developing fear and in emotion regulation (Adolphs, 2004). Pardini et al. (2014) found lower amygdala volumes to be associated with aggression. Our finding of a larger amygdala volume in aggression is therefore novel in the literature.

Studies comparing persons with schizophrenia with higher or lower aggression scores in questionnaires found larger volumes in the caudate nucleus and the OFC in persons with schizophrenia with a higher versus those with a lower aggression score. There are contradictory results concerning the OFC and the caudate nucleus - these contradictions may be due to different study designs (continuous versus categorical measures). Also, effects of medication could play an important role. In our effect-size analyses we found that VS as opposed to NVS showed significantly lower WB volumes.

4.2 Functional Magnetic Resonance Imaging Correlates of Aggression in Psychoses

Despite the importance of the topic, only a limited number of studies on functional MRI correlates of aggression have been performed. When comparing violent as opposed to non-violent persons with schizophrenia in working memory tasks, VS hypoactivated their right inferior parietal lobe - an area known for being involved in working memory tasks, but not in aggression.

We hypothesize that this hypoactivation may represent a working memory dysfunction in the VS group.

In face affect recognition tasks, VS with high versus low psychopathy scores hyperactivated the right amygdala when viewing facial expressions of disgust. To our knowledge, there are no previous studies on this matter - this makes it difficult to integrate these findings. VS with high as opposed to low psychopathy scores hypoactivated the right amygdala when seeing fearful faces. In healthy controls, fearful faces are known to hyperactivate the amygdala - there are no studies on activation patterns in aggressive healthy controls in this matter. In general, persons with schizophrenia hypoactivate the amygdala in response to emotional stimuli.

In emotion induction paradigms, VS as opposed to NVS hyperactivated the right middle frontal gyrus, inferior parietal gyrus, medial prefrontal gyrus, anterior cingulate, lingual gyrus, globus pallidus, mid-cingulate, precuneus, cuneus, middle temporal gyrus, inferior temporal gyrus and the left middle occipital gyrus and cerebellar tuber.

In a task on affective theory of mind, VS as opposed to NVS hyperactivated the left inferior frontal gyrus and the left superior temporal sulcus. The activation in the inferior frontal gyrus is compatible with a challenge in language comprehension, while the superior temporal sulcus is known to be impaired in social perception and general theory of mind.

4.3 Limitations with Recommendations for Future Research

In the following sections we outline the various factors that limit the explanatory power of our work. As the limitations of our two systematic reviews are very similar, we summarize them.

4.3.1 Operationalizing Aggression

In most of our reviewed articles, history of violence was not sufficiently specified and both type and scale of the violent acts remain unclear. Future studies should clearly define and quantify nature and extent of aggressive behaviour.

4.3.2 Sample Sizes

Our reviews suffer from small sample sizes and considerable cohort overlaps - therefore, we could not calculate meta-analyses and it was not possible to estimate publication bias. We suggest future research should focus on replicating or refuting previous findings, or at least include replication as an additional aim of study.

4.3.3 Predictors and Moderators of Aggression in Psychosis

Important influencing factors like psychopathology, general intelligence, substance use or effect of medication have often not been reported. Therefore, we could not correct for these factors in our analyses - we suggest future studies to report these important mediators clearly in order to allow for analyses of these covariates.

4.3.4 Affective Psychoses and Early Psychoses: Neglected Areas

Although these groups of persons are known to be at an increased risk for aggressive behaviour just as persons with non-affective psychoses, there are no studies reporting structural or functional correlates of aggression. The disregard for these diagnostic groups severely limits our understanding of aggression in psychotic disorders. We therefore recommend that future studies include persons with affective psychoses or early stages of psychoses taking into account the above mentioned recommendations.

4.3.5 Functional Magnetic Resonance Imaging as Technique to Investigate Biological Underpinnings of Aggression in Psychosis

Functional magnetic resonance imaging is currently the best tool for measuring functional organization of the brain. Still, it provides no direct measure of brain activity. fMRI cannot easily differentiate between bottom-up and top-down signals and excitation or inhibition (Logothetis, 2008). We therefore have to be careful when interpreting results and drawing conclusions about brain function. Furthermore fMRI provides us with maps we do not really understand: As fMRI measures brain activity indirectly, we do not know whether the maps of activation really mean that the respective brain areas are truly involved in the feature of interest (Logothetis, 2008). Combining fMRI with another mesaure, for example EEG, might reduce uncertainties concerning the activation of brain areas. Furthermore, combining these two methods provides the advantage of improving the temporal resolution of the data.

4.4 Voxel-Based Morphometry Correlates of Aggression in Early Psychosis

Our voxel-based morphometry study showed that individuals in early stages of psychosis with an agitated-aggressive syndrome have significant volumetric reductions in the lingual gyrus as opposed to healthy controls. These reductions were not evident when comparing the aggressive with the non-aggressive participants. This finding does not fit any previously described volumetric correlate of aggression in early psychosis. Independently of a psychotic disorder, Soloff et al. (2014) examined structural correlates of aggression in patients with borderline personality disorder and found that high as opposed to low lethality suicide attempters had diminished grey matter in the left lingual gyrus. The authors discuss that these grey matter reductions may impair social functioning (Soloff, White, & Diwadkar, 2014). In the following, we outline several limitations of our study:

- Group differences: Our patient groups significantly differed in the intake of antidepressants and consumption of nicotine. Due to our small sample size, we could not correct for this potential bias and therefore cannot exclude that the reported differences in brain volumes may have been affected by substance use.

- Influencing variables: Some potentially important moderators of aggression were not available, e.g. forensic history, antisocial personality disorder.

- Dichotomizing the groups: Dichotomizing the patient group using a median split may not be an ideal approach. According to our median split, patients with BPRS-EC high scores from 4 to 5 were entered in the low aggression group, while all others were entered in the high aggression group. A score of 4 corresponds to complete absence of agitation and aggression, and a score of 5 to nearly complete absence of aggression. Therefore, the median split corresponds to a dichotomization into a group with near complete absence and with the presence of an agitated-aggressive syndrome.

- Pooling ARMS and FEP as one group: the ARMS-status is not a very specific indicator for transition to psychosis. It seems the at-risk mental state might rather be a more general indicator for a psychiatric disease.

- Our high and low aggression subgroups also significantly differed in BPRS and SANS total scores, and it is known that psychopathological symptoms are often interrelated: this further raises the question how specific our results were. Therefore, it remains unclear whether the observed volumetric reductions are specific to an agitated-aggressive syndrome.

- The results would not hold if an initial peak-level threshold of $p < 0.001$ had been chosen.

Due to these limitations, this study has to be considered a pilot study presenting the first hint towards a structural correlate of an agitated-aggressive syndrome in ARMS and FEP, and replication studies are needed in order to evaluate this finding.

5 Conclusion

We reviewed the evidence on structural as well as functional magnetic resonance imaging correlates of aggression in psychosis. We found nonsystematic structural and functional correlates of aggression in schizophrenia. Only very few studies have been conducted, all using varied paradigms and often overlapping samples. Our study on correlates of aggression in early stages of psychoses lead to the hypothesis that the left lingual gyrus volume may be inversely correlated with an agitated-aggressive syndrome in early psychoses. This still has to be evaluated with replication studies. At this point, the MRI studies at hand do not yet allow for a deeper understanding of the neurobiological underpinnings of aggression in psychoses. When exploring novel study protocols and paradigms, research should seek to improve upon and enhance previous findings using a hypothesis driven approach.

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Structural Magnetic Resonance Imaging Correlates of Aggression in Psychosis: A Systematic Review and Effect Size Analysis

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Background: Aggression in psychoses is of high clinical importance, and volumetric MRI techniques have been used to explore its structural brain correlates.

Methods: We conducted a systematic review searching EMBASE, ScienceDirect, and PsycINFO through September 2017 using thesauri representing aggression, psychosis, and brain imaging. We calculated effect sizes for each study and mean Hedge's g for whole brain (WB) volume. Methodological quality was established using the PRISMA checklist (PROSPERO: CRD42014014461).

Results: Our sample consisted of 12 studies with 470 patients and 155 healthy controls (HC). After subtracting subjects due to cohort overlaps, 314 patients and 96 HC remained. Qualitative analyses showed lower volumes of WB, prefrontal regions, temporal lobe, hippocampus, thalamus and cerebellum, and higher volumes of lateral ventricles, amygdala, and putamen in violent vs. non-violent people with schizophrenia. In quantitative analyses, violent persons with schizophrenia exhibited a significantly lower WB volume than HC ($p = 0.004$), and also lower than non-violent persons with schizophrenia ($p = 0.007$).

Conclusions: We reviewed evidence for differences in brain volume correlates of aggression in persons with schizophrenia. Our results point toward a reduced whole brain volume in violent as opposed to non-violent persons with schizophrenia. However, considerable sample overlap in the literature, lack of reporting of potential confounding variables, and missing research on affective psychoses limit our explanatory power. To permit stronger conclusions, further studies evaluating structural correlates of aggression in psychotic disorders are needed.

Keywords: aggression, psychosis, structural magnetic resonance imaging, systematic review, effect size analysis

INTRODUCTION

Aggression in Persons With Psychotic Disorders

Defining Aggression

Aggression, defined as hostile or destructive behavior, can be classified by the target of aggression (self-directed or directed at others), the mode of aggression (physical or verbal), or the cause of aggression (1).

We distinguish premeditated vs. impulsive aggression. Premeditated aggression represents a planned behavior while impulsive aggression occurs as a response to provocation or stress (2, 3). Impulsive aggression following a dangerous threat is part of normal defensive behavior—if the aggressive response is exaggerated in relation to the provocation, impulsive aggression becomes pathological (1).

Epidemiology and Risk Factors of Aggression in Persons With Psychotic Disorders

Persons with psychoses are at increased risks for violent behavior (4–6) even in the first episode of illness (7–10) and in at-risk mental states (11), although more than 90% of violent acts in society are committed by persons without psychoses (12). Brekke et al. (13) even found that people with schizophrenia are at a greater risk of becoming victims of violence than of being an offender. Still, according to Wehring and Carpenter (14), a focus on criminal records underestimates the prevalence of aggressive behavior in schizophrenia.

In a meta-analysis including 110 studies, Witt et al. (15) examined risk factors of violence in persons with psychotic disorders. About 88% of the persons in the included studies had been diagnosed with schizophrenia. The authors found the following elements to be associated with violence risk: hostile behavior, poor impulse control, lack of insight, recent alcohol or drug misuse, and non-adherence with psychological or pharmacological therapies (15). Criminal history was more strongly associated with violence than substance misuse or demographic factors (15). Moreover, economic deprivation, violent victimization, childhood conduct problems, and sexual abuse are known common risk factors favoring aggression (16). Witt et al. (15) reported victimization to be one of the strongest risk factors.

Structural MRI Findings in Psychoses

Structural Brain Alterations in Persons With Psychoses

Schizophrenia is associated with ventricular enlargement and reductions in frontal and temporal lobe gray matter (GM) (17, 18). Furthermore, structural abnormalities in schizophrenia appear to include a smaller amygdala, hippocampus, and parahippocampus (19, 20). Goodkind et al. (21) performed a large-scale voxel-based meta-analysis on GM abnormalities in different psychiatric diseases including schizophrenia. They reported increased GM in the striatum in patients as opposed to controls. Decreased GM was observed in the bilateral anterior insula, dorsal anterior cingulate (AC), dorsomedial prefrontal cortex, ventromedial prefrontal cortex, thalamus, amygdala, hippocampus, superior temporal gyrus, and parietal operculum.

A meta-analysis indicated the occurrence of GM reductions in temporal, AC, cerebellar, and insular regions, in a first psychotic episode (22).

Strakowski et al. (23) detected increased volumes of amygdala, thalamus, and globus pallidus in affective psychoses. Altshuler et al. (24) and Brambilla et al. (25) confirmed only the increase in amygdala volume. A meta-analysis of gray matter alterations in bipolar disorder by Wise et al. (26) revealed significantly smaller GM volumes in patients relative to controls in the bilateral insula, superior temporal gyrus, medial prefrontal gyrus, and the anterior cingulate. Enlarged volumes were found in cerebellar regions, the bilateral middle frontal gyrus, the right middle and inferior temporal gyrus, and the right middle occipital gyrus.

In summary, there is ample evidence for structural abnormalities in schizophrenia, with the most robust findings showing an enlargement of the lateral ventricles (LV) and a volume reduction of the left superior temporal gyrus and the frontal brain, mainly in the prefrontal and orbitofrontal regions (27). However, a GM increase in the striatum and GM reductions in several other key structures have also repeatedly been reported. Literature on affective psychoses supports the existence of structural differences with GM increase (e.g., concerning the amygdala) as well as decrease (including the medial prefrontal and insular cortex) compared to controls.

Effects of Antipsychotic Medication

Antipsychotics may affect progressive brain changes during the course of the illness (28, 29). Fusar-Poli et al. (30) observed that at baseline, patients showed smaller whole brain volumes and larger LV than controls. There were progressive GM volume reductions and LV enlargements in patients but not in controls, even when controlling for illness-related factors. Antipsychotic medication has also been shown to increase striatal GM, explaining the finding of increased striatal GM in individuals with schizophrenia (21). In their meta-analysis, Goodkind et al. (21) reported no association between antipsychotic medication and insular volume. However, despite this emerging literature, the relationship between structural alterations, illness-, and treatment-related factors has not yet been sufficiently disentangled.

Structural MRI Findings in Aggression

Structural MRI Correlates of Aggression in Healthy Persons

Matthies et al. (31) observed a negative correlation between amygdala volumes and aggression scores in healthy volunteers.

Sakuta and Fukushima (32) and Bufkin et al. (33) found the prefrontal cortex and medial temporal regions to be associated with aggression and explained their findings in the context of negative emotion regulation.

Structural MRI Correlates of Aggression in Patient Populations

Most of the research on structural correlates of aggression is based on patients with antisocial personality disorder or psychopathy.

Yang and Raine (34), in a meta-analysis, found reduced right orbitofrontal cortex (OFC), right anterior cingulate cortex,

and left dorsolateral prefrontal cortex volumes in antisocial individuals.

In a review, Weber et al. (35) reported volume loss in prefrontal and right superior temporal gyrus, in the amygdala, and in the posterior hippocampus, as well as an increase in callosal white matter volume, in psychopaths. Psychopathy may be associated with brain abnormalities in a prefronto-temporo-limbic circuit—regions involved in emotional and learning processes (35).

Wahlund et al. (36) reported in a review that some studies showed smaller volumes in temporal regions, and some in frontal regions, while others found no differences. Raine et al. (37) observed increased corpus callosum volume in highly psychopathic antisocial subjects compared to that of healthy controls.

Aoki et al. (38) conducted a voxel-based meta-analysis on structural correlates in persons with antisocial behavior. They reported significantly smaller GM volumes in the left superior frontal gyrus, the left anterior insula, and the right lentiform nucleus in individuals with antisocial behavior, as compared to healthy controls. Larger volumes were reported in the right fusiform gyrus, the right inferior parietal lobule, the left superior parietal lobule, the right cingulate gyrus, and the right postcentral gyrus. In summary, findings regarding structural correlates of aggression in patients suggest a reduction in prefrontal and temporal volume as compared to healthy controls.

Preliminary Work on Structural MRI Correlates of Aggression in Patients With Psychoses

Relatively few studies have examined structural MRI correlates of aggression in psychoses. Reviews have attempted to compile the available data: Naudts and Hodgins (39) observed that violent as opposed to non-violent persons with schizophrenia have impaired orbitofrontal functioning and hypothesize that structural brain abnormalities may exist in the amygdala-orbitofrontal system and in the prefrontal cortex and hippocampus. Soyka (27) and Hoptman et al. (40) state that frontal and temporal abnormalities are a consistent feature of aggression in schizophrenia.

In summary, published reviews suggest that there are structural alterations in aggressive, psychotic individuals. However, literature regarding affective psychoses is sparse. Existing reviews were conducted 5 or more years ago and are narrative expert reviews that lack systematic literature searches as well as reports of effect sizes. No systematic review (i.e., according to the PRISMA guidelines) or effect size analysis has been conducted on the topic to date.

Objective and Research Question

Considering the high clinical importance of aggression in psychoses and the state of the literature, our aim was to conduct a systematic literature search, to compile all available data on structural MRI correlates of aggression in patients with psychotic disorders, and to calculate effect sizes of the observed differences. More specifically, we aimed at identifying structural magnetic resonance imaging differences in brain volumes between violent vs. non-violent persons with psychoses.

METHODS

To achieve a high standard of reporting we adopted the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines (41) and the revised "Quality of Reporting of Meta-analyses" QUORUM statements (42). We registered the detailed study protocol on the International Prospective Register of Systematic Reviews database (PROSPERO; registration number: CRD42014014461) prior to the completion of data extraction (43). We assessed methodological quality using the PRISMA 2009 checklist (41). Out of 27 items, 23 were fulfilled, indicating an overall high methodological quality.

Quality Assessment

Quality of the studies was assessed using an item-checklist constructed specifically for the current work, similar to the quality assessment described by Paulson and Bazemore (44) and adapted by Fusar-Poli et al. (30). We rated precision, directness, and consistency of the data. The quality assessment categories are listed in Supplementary Table 1 (0–2 points per item, with a theoretical range of 0–38 for the total quality score). The included studies were characterized as high-quality (above 80% of the maximal sum of points), moderate-high (60–79%), moderate (40–59%), moderate-low (20–39%), and low-quality studies (below 19%). Nine of the 12 studies included in the meta-analysis had a moderate-high quality and three had a moderate quality.

Established and adapted quality checklists tend to reference the current state of the literature to at least some degree, and quality assessments of the included studies were rated as low to high quality with respect to the currently published manuscripts. For example, none of the published studies in the field has used longitudinal study designs, and controlling for lifetime substance use disorder is a difficult challenge not yet adequately met. Both factors would have further improved the quality of the included studies, but they are not currently accounted for in the quality assessment checklists.

Search and Selection Strategy

We first conducted a systematic review of structural MRI studies on correlates of aggression in psychotics vs. healthy controls. We searched the PubMed, EMBASE, ScienceDirect, and PsycINFO databases, with no restriction on the publication start date range, and searched for publications through September 2017. We used search thesauri representing aggression, psychosis and brain imaging. The detailed search terms are available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014461. Furthermore, we searched the reference lists of all of the selected original articles for additional literature.

We screened all studies according to the following inclusion criteria. We included longitudinal, cross-sectional, and case-control studies (journal articles, book chapters, and dissertations)

reporting brain imaging correlates of aggression, comparing: (1) affective or non-affective psychosis groups with a history of violence, or including continuous measures of aggression, (2) affective or non-affective psychosis groups with a history of violence or including continuous measures of aggression, compared to healthy controls, (3) affective or non-affective psychosis groups with a history of violence or including continuous measures of aggression, compared to controls with diagnoses other than affective or non-affective psychoses, (4) affective or non-affective psychosis groups with a history of violence compared to affective or non-affective psychosis groups without a history of violence. Furthermore, we included all brain imaging studies using structural MRI with an age of cases and controls of at least 18 years. We applied no language restriction and required patients to have an established diagnosis of affective or non-affective psychosis according to DSM or ICD.

If there was insufficient information to extract the necessary data, we excluded the study. For the quantitative analyses, we excluded studies with no comparison group or with an overlap of more than 10% with the cases or controls reported in other studies selected, in which case, we then excluded the study with the smaller sample size. The entire process was conducted independently by two reviewers (SW, HAJ). In case of disagreement, reviewers discussed their reasons for inclusion or exclusion. If consensus was not reached, a third reviewer (CGH) was included, in order to reach a decision.

Data Extraction

The main outcome measure was whole brain volume of the two patient groups [violent persons with schizophrenia (VS) and non-violent persons with schizophrenia (NVS)] and healthy controls (HC), while the additional outcome measures were the specific regional volumes of the mentioned groups, reported in *mean* and *standard deviation (SD)*.

We extracted the following information from all studies: imaging center, first author, year of publication, type of imaging analysis, population characteristics of the healthy controls and patient groups (group size, gender, age, psychopathology, IQ, medication), and diagnosis. For an overview, see **Table 1**. All corresponding authors of the included publications were contacted by email using a standardized questionnaire for completing our coding sheets collecting means and standard deviations of whole brain volumes and specific regional volumes of all examined groups, as well as descriptive information about subjects.

SW and HAJ independently searched the databases and extracted the relevant data in order to avoid bias or error in article selection and information coding.

Data Analysis

First, we performed a qualitative analysis of all included publications. Second, in a meta-analytic approach, we calculated (a) effect size separately for each study and (b) mean Hedge's g for global brain volume measurements and regions of interest including volumetric and morphometric results. All analyses were performed with "Statistical Package for Social Sciences" (IBM SPSS Statistics for Windows, version 23.0, IBM Corp., Armonk, NY, USA).

Group Comparisons

We performed a one-way ANOVA to describe group characteristics with regard to sample size, gender, age, and IQ.

Meta-Analysis

For computations, we used the SPSS macros written by Lipsey and Wilson (47). We calculated the pooled standard deviation, then standardized the mean effect size from statistical information reported in the studies. Due to small sample sizes (samples with less than 20 subjects) we corrected for this bias using Hedge's method, to receive an unbiased effect size estimate. We then calculated the effect size for each study separately using the unbiased effect size estimate. Finally, we weighted the effect size depending on each group's sample size.

RESULTS

Literature Search

The initial literature search identified 1177 possible studies of interest. After screening all studies and applying inclusion and exclusion criteria, 1148 studies were excluded. Using the template of the PRISMA flow diagram, the study selection procedure is summarized in **Figure 1**. We found no studies including subjects with affective psychoses.

The final sample consisted of 12 studies with a total of 470 patients and 155 HC. After subtracting subject overlaps due to the publication of multiple papers using the same cohort, the sample consisted of 314 patients and 96 HC.

Table 1 gives an overview of all included studies showing the imaging center, name of the first author, year of publication, type of imaging analysis, population characteristics of HC, patient groups (group size, gender, age, psychopathology, IQ, medication), and diagnosis, also indicating sample overlap where applicable.

Sample Descriptives

Among the included 12 studies, there were no significant differences in sample sizes, age or gender across the groups (see **Table 2**). Regarding WAIS IQ we found significant differences between HC and NVS as well as VS. NVS and VS did not significantly differ in IQ (see **Table 2**). Missing data impeded calculation of differences regarding antipsychotic medication or psychopathology.

Aggression Operationalized as "History of Violence"

Barkataki et al. (45), Kumari et al. (48–50), Narayan et al. (51), Del Bene et al. (53), Puri et al. (54), Kuroki et al. (55), Schiffer et al. (56), and Yang et al. (57) used the following three groups to examine aggression in schizophrenia: (1). Healthy, non-violent controls (HC), (2). Non-violent persons with schizophrenia (NVS), and (3). Violent persons with schizophrenia (VS).

TABLE 1 | Overview of the studies included in the qualitative report, describing the imaging center; name of the first author; year of publication; type of imaging analysis; population characteristics of the healthy controls and patient groups (group size, gender, age, psychopathology, violence score IQ, medication); diagnosis.

Imaging Center	References	Type of sMRI analysis	HC: N male/female Age: mean/SD Violence Score: mean/SD IQ: mean/SD	NVS Patients: N male/female Age: mean/SD Psychopathology: mean/SD Violence Score: mean/SD IQ: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	VS Patients: N male/female Age: mean/SD Psychopathology: mean/SD Violence Score: mean/SD IQ: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	Operationalization of Aggression	Sum of Points in Quality Assessment of Individual Studies (maximum points: 38)	Diagnosis
Institute of Psychiatry and Maudsley Hospital, London and Broadmoor Special Hospital, Berkshire, England	Barkataki et al. (45)	sMRI—ROIs: Cerebellum Temporal lobe Lateral ventricles Caudate nucleus Putamen Thalamus Hippocampus Amygdala	15 15/0 32.1/7.5 Gunn & Robertson Scale: 0.50/0.85 NART IQ: 106.9/16.1 WAIS IQ: 104.3/14.5	15 15/0 34.5/7.5 PANSS: Positive symptoms: 12.0/3.9 Negative symptoms: 20.1/5.4 General psychopathology: 32.7/5.8 Total Score: 64.8/12.2 Gunn & Robertson Scale: 1.20/1.32 NART IQ: 98.9/13.4 WAIS IQ: 89.3/13.5 Medication: 567.0/323.5	13 13/0 34.5/4.9 PANSS: Positive symptoms: 10.8/4.9 Negative symptoms: 17.8/5.2 General psychopathology: 23.8/5.6 Total Score: 52.8/13.11 Gunn & Robertson Scale: 6.15/1.46 NART IQ: 96.4/13.9 WAIS IQ: 85.0/12.1 Medication: 426.7/227.6	History of Violence: Detained in secure conditions with the following index offenses: 5 homicides, 2 attempted murders, 4 injuries, 1 robbery, and 1 "other type of serious violence"	27	DSM-IV SCID: paranoid, undifferentiated, disorganized and residual subtypes of schizophrenia
	Kumari et al. (48)	VBM	14 14/0 32.1/7.7 Gunn & Robertson Scale: 0.47/0.84 NART IQ: 106.8/16.6	14 14/0 33.8/4.8 PANSS: Positive symptoms: 12.1/4.1 Negative symptoms: 20.3/5.5 General psychopathology: 33.2/5.6 Gunn & Robertson Scale: 1.29/1.33 NART IQ: 93.7/14.9 Medication: 539.2/299.8	10 10/0 35.0/7.5 PANSS: Positive symptoms: 10.2/2.9 Negative symptoms: 17.0/4.3 General psychopathology: 24.5/4.0 Gunn & Robertson Scale: 6.30/1.34 NART IQ: 98.7/13.9 Medication: 407.8/152.2	History of Violence: a score of 5 or above on the Gunn and Robertson Scale indicating at least one fatal or near fatal act of violence against the victim	27	DSM-IV SCID: schizophrenia

(Continued)

TABLE 1 | Continued

	Kumari et al. (49)	sMRI—ROIs: Whole brain Cerebellum Temporal lobe Lateral ventricles Caudate nucleus Putamen Thalamus Hippocampus Amygdala Prefrontal and occipitoparietal regions	15 15/0 32.1/7.5 Gunn & Robertson Scale: 0.47/0.83 NART IQ: 106.9/16.1	15 15/0 34.4/7.0 PANSS: Positive symptoms: 12.0/4.1 Negative symptoms: 20.1/5.3 General psychopathology: 32.7/6.0 Total Score: 64.8/12.5 Gunn & Robertson Scale: 1.2/1.27 NART IQ: 98.9 / 10.9 Medication: 543.1 / 294.0	13 13/0 34.7/4.2 PANSS: Positive symptoms: 10.8/5.1 Negative symptoms: 17.8/4.6 General psychopathology: 23.8/5.7 Total Score: 52.9/12.6 Gunn & Robertson Scale: 6.16/1.52 NART IQ: 96.4 / 14.5 Medication: 430.0 / 245.3	History of Violence: a score of 5 or above on the Gunn and Robertson Scale indicating at least one fatal or near fatal act of violence against the victim	27	DSM-IV SCID: schizophrenia
	Kumari et al. (50)	sMRI—ROI: Anterior Cingulate	15 15/0 32.1/7.5 Gunn & Robertson Scale: 0.47/0.83 NART IQ: 106.9/16.1	15 15/0 34.5/6.9 Not reported Gunn & Robertson Scale: 1.2/1.27 NART IQ: 98.9 / 10.9 Medication: 543.1 / 294.0	13 13/0 32.06/5.7 Not reported Gunn & Robertson Scale: 3.61/1.16 NART IQ: 100.5 / 14.3 Medication: 430.0 / 245.3	History of Violence: a score of 5 or above on the Gunn and Robertson Scale indicating at least one fatal or near fatal act of violence against the victim	27	DSM-IV SCID: schizophrenia
	Narayan et al. (51)	cortical thickness estimation	15 15/0 32.1/7.5 Not reported Not reported	15 15/0 34.5/7.5 Not reported Not reported Not reported Not reported	12 12/0 34.4/5.2 Not reported Not reported Not reported Not reported	History of Violence: a score of 5 or above on the Gunn and Robertson Scale indicating at least one fatal or near fatal act of violence against the victim	27	DSM-IV SCID: schizophrenia
Nathan Kline Institute at Rockland Psychiatric Center, Orangeburg, NY, USA Dorothea Dix Hospital, North Carolina, USA	*Hoptman et al. (46)*	VBM	No HC group	Total patient group: 49 43/6 41.5/8.2 Not reported Not reported Not reported Not reported		Overt Aggression Scale (OAS) & PANSS "Hostility"	18	DSM-IV SCID: schizophrenia and schizoaffective disorder

(Continued)

TABLE 1 | Continued

	Hoptman et al. (52)	VBM	No HC group	Total patient group: 49 43/6 41.5/8.2 Not reported Total Aggression Score (of OAS): 6.83/17.6 PANSS Hostility Score: 2.05/1.28 Not reported Not reported	OAS & PANSS "Hostility"	18		DSM-IV SCID: schizophrenia and schizoaffective disorder
	Del Bene et al. (53)	sMRI—ROIs: Amygdala Hippocampus Thalamus Whole brain Ventricular volumes	24 19/5 30.0/2.1 LHA: 13.8/1.3 Barratt Impulsivity: 55.1/1.8 BPAQ Total: 56.5/2.7 BPAQ physical: 15.4/1.0 BPAQ Verbal: 13.1/0.9 BPAQ Anger: 11.7/0.6 BPAQ Hostility: 16.1/1.1 IQ WRAT-4: 50.3/1.8	26 20/6 43.1/1.9 PANSS: Total score: 78.5/14.2 General score: 38.7/1.5 Positive symptoms: 18.7/5.4 Negative symptoms: 21.1/5.3 LHA: 10.3/0.9 Barratt Impulsivity: 61.3/2.5 BPAQ Total: 63.9/4.2 BPAQ physical: 15.6/1.4 BPAQ Verbal: 11.9/0.9 BPAQ Anger: 14.4/1.1 BPAQ Hostility: 20.9/1.7 IQ WRAT-4: 42.1/2.1 1343.7/687.4	37 31/6 35.3/1.6 PANSS: Total score: 79.1/12.9 General score: 40.5/1.2 Positive symptoms: 20.7/6.4 Negative symptoms: 17.9/5.4 LHA: 25.6/0.9 Barratt Impulsivity: 62.3/1.8 BPAQ Total: 77.1/3.0 BPAQ physical: 22.3/1.2 BPAQ Verbal: 14.1/0.8 BPAQ Anger: 18.2/1.1 BPAQ Hostility: 22.0/0.9 IQ WRAT-4: 45.1/1.2 1230.6/637.8	History of Violence: LHA, BPAQ, BIS	25	DSM-IV SCID: schizophrenia
Hammersmith Hospital, London, England	Puri et al. (54)	VBM	No HC group	13 10/3 32.6/2.5 Not reported Not reported Not reported Not reported	13 12/1 40.4/3.7 Not reported Not reported Not reported Not reported	History of Violence: "violent offending including homicide, attempted murder or wounding with intent to cause grievous bodily harm"	19	DSM-IV SCID: schizophrenia

(Continued)

TABLE 1 | Continued

National Center of Neurology and Psychiatry Hospital, Tokyo, Japan	Kuroki et al. (55)	VBM		No HC group	23 23/0 36.8/11.0 PANSS: Positive symptoms: 9.4/3.6 Negative symptoms: 14.7/6.2 Disorganization: 6.8/3.7 Depressive: 7.0/3.2 Excitement: 6.7/3.0 not reported not reported 477.38/434.8	34 34/0 40.6/9.5 PANSS: Positive symptoms: 12.2/4.8 Negative symptoms: 17.1/7.0 Disorganization: 8.4/3.2 Depressive: 6.7/2.6 Excitement: 8.3/3.5 not reported not reported 706.9/606.4	History of Violence: serious violent acts hospitalized in a forensic clinic	28	DSM-IV SCID: schizophrenia
Division of Forensic Psychiatry, Department of Psychiatry, Psychotherapy and Preventive Medicine, University Hospital, Ruhr-University Bochum, Bochum, Germany	Schiffer et al. (56)	VBM		25 25/0 33.0/10.0 Violence: Mean score life history of aggression (0-55): 11.2/4.3 Mean number of criminal convictions: 0.0/0.0 Premorbid IQ: 109/13	23 23/0 35.7/8.7 PANSS: Total score: 63.7/17.2 General score: 31.9/8.3 Positive symptoms: 13.6/4.8 Negative symptoms: 17.5/6.7 Violence: Mean score life history of aggression (0-55): 9.5/3.4 Mean number of criminal convictions: 0.0/0.0 Premorbid IQ: 102/13 616/418	27 27/0 36.2/7.7 PANSS: Total score: 63.0/14.1 General score: 31.3/6.9 Positive symptoms: 14.4/4.0 Negative symptoms: 17.2/6.4 Violence: Mean score life history of aggression (0-55): 24.6/11.2 Mean number of criminal convictions: 4.4/5.6 Premorbid IQ: 101/15 577/296	History of Violence: "conduct disorder prior to age 15; number of conduct disorder symptoms, antisocial personality disorder, mean score life history of aggression, mean number of criminal convictions"		DSM-IV SCID: schizophrenia
Nanjing Brain Hospital in Nanjing, China	Yang et al. (57)	sMRI—ROIs: superior frontal gyrus middle frontal gyrus inferior frontal gyrus middle orbitofrontal gyrus lateral orbitofrontal gyrus gyrus rectus parahippocampal gyrus hippocampus	32 4/28 32.0/9.9 Not reported WAIS IQ: 101.5/15.1	19 3/16 33.1/10.1 Not reported Not reported WAIS IQ: 86.6/17.7 Not reported	22 3/19 34.7/13.0 Not reported Not reported WAIS IQ: 84.9/14.4 Not reported	History of Violence: "detainees accused of homicide undergoing forensic psychiatric evaluation"	25	DSM-IV SCID & CCMD-3: schizophrenia	

MRI, magnetic resonance imaging; sMRI, structural magnetic resonance imaging; VBM, voxel based morphometry; ROI, region of interest; HC, healthy controls; NVS, non-violent schizophrenia group; VS, violent schizophrenia group; HoV, History of Violence; PANSS, Positive and Negative Syndrome Scale; NART IQ, National Adult Reading Test for estimating premorbid intelligence levels; WAIS IQ, Wechsler Adult Intelligence Scale to measure cognitive ability in adults, Gunn & Robertson Scale, 5-item scale for rating violence and other criminal activities; Overt Aggression Scale OAS, 6-item scale for rating aggression (from verbal to physical); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders: fourth edition; SCID, Structured Clinical Interview for DSM disorders; CCMD-3, Chinese Classification of Mental Disorders, third edition; LHA, Life History of Aggression; BPAQ, Buss-Perry Aggression Questionnaire; BIS, Barratt Impulsiveness Scale. Articles with author names marked in blue or in italic, respectively; used the same cohort, of which the work by Barkataki et al. (45) and Hoptman et al. (46), respectively, were the underlying primary studies.

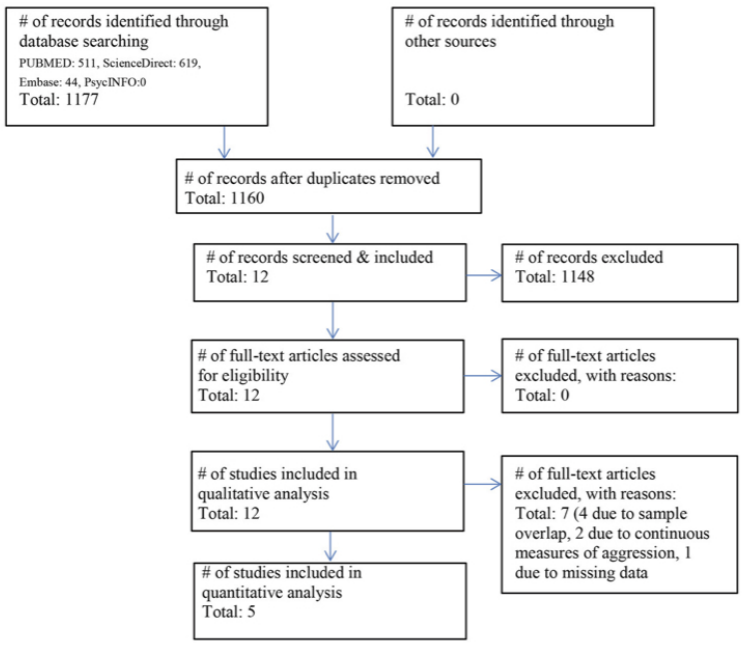


FIGURE 1 | Flowchart of the literature search and included studies according to the PRISMA guidelines (41).

TABLE 2 | Descriptive statistics of healthy control group (HC), non-violent schizophrenia patients (NVS), and violent schizophrenia patients (VS) over all 12 included studies, with the exclusion of overlapping cohorts.

	HC *M (SD)*	NVS *M (SD)*	VS *M (SD)*	Group differences (ANOVA) *p*
Sample size	24.0 (6.9)	20.4 (4.9)	24.4 (9.3)	0.568
Average % male	72.9 (41.4)	79.6 (30.0)	82.5 (31.1)	0.898
Age	31.7 (1.2)	36.7 (4.1)	37.6 (3.1)	0.033
IQ	102.9 (2.0)	88.0 (1.9)	84.9 (0.1)	0.003^{+}

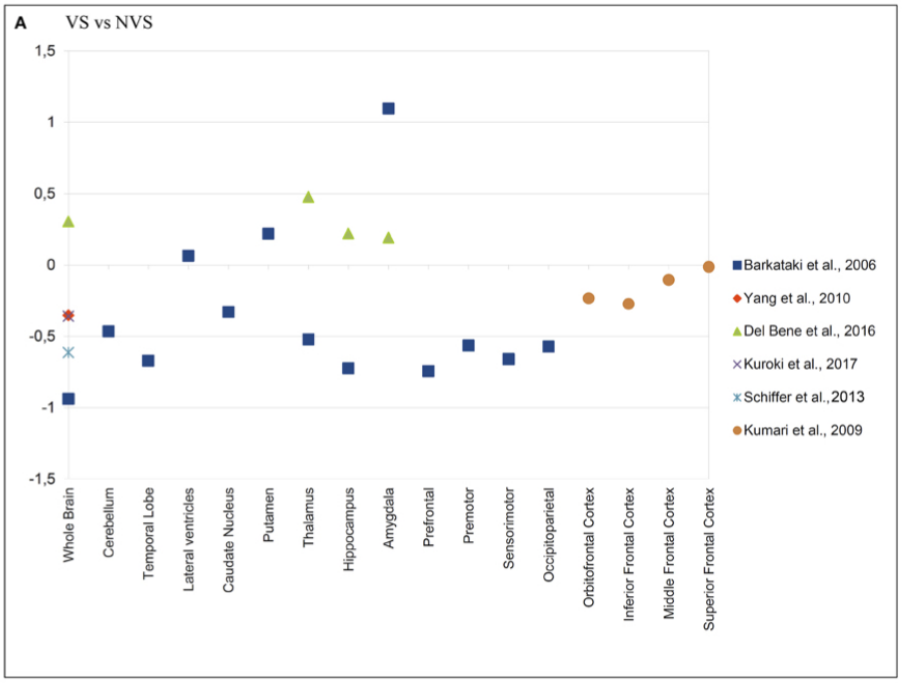
HC, healthy control group; NVS, non-violent schizophrenia patients; VS, violent schizophrenia patients; M, mean; SD, standard deviation. Note. $^{+}$The group comparisons VS vs. HC and NVS vs. HC showed significant group differences in IQ [$F_{(2,\ 3)} = 73.119$] while the groups VS vs. NVS did not differ significantly in IQ.

Kumari et al. (48–50), Narayan et al. (51) published work based on the cohort originally examined by Barkataki et al. (45). As part of the quantitative analyses, we calculated effect sizes for the comparison of HC vs. NVS, HC vs. VS, and NVS vs. VS where applicable. For an overview of effect sizes for each area, see **Figure 2**.

Violent vs. Non-violent Persons With Schizophrenia

Most studies found decreased volumes in VS vs. NVS (45, 48, 49, 51, 54, 55, 57) while others found increased volumes in VS as opposed to NVS (49, 53, 56). For an overview, see **Table 3**.

More specifically, Barkataki et al. (45) found that VS had a significantly reduced whole-brain volume compared to NVS. The VS group showed significantly larger putamen and smaller amygdala volumes than the NVS group—these findings, however, were not sustained when covarying for Positive and Negative Syndrome Scale (PANSS) general psychopathology score. In the study by Kumari et al. (48), temporal lobe and hippocampal volume were reduced in VS compared to NVS at a trend level. Kumari et al. (49) found that VS had smaller whole brain, temporal lobe, and hippocampus volumes than NVS. However, VS had larger amygdala volumes than NVS. When comparing the AC volumes of VS with NVS, there was no significant difference (50). Narayan et al. (51) found reduced cortical thickness in the right ventromedial prefrontal and lateral sensorimotor cortex in aggressive vs. non-aggressive people with schizophrenia.



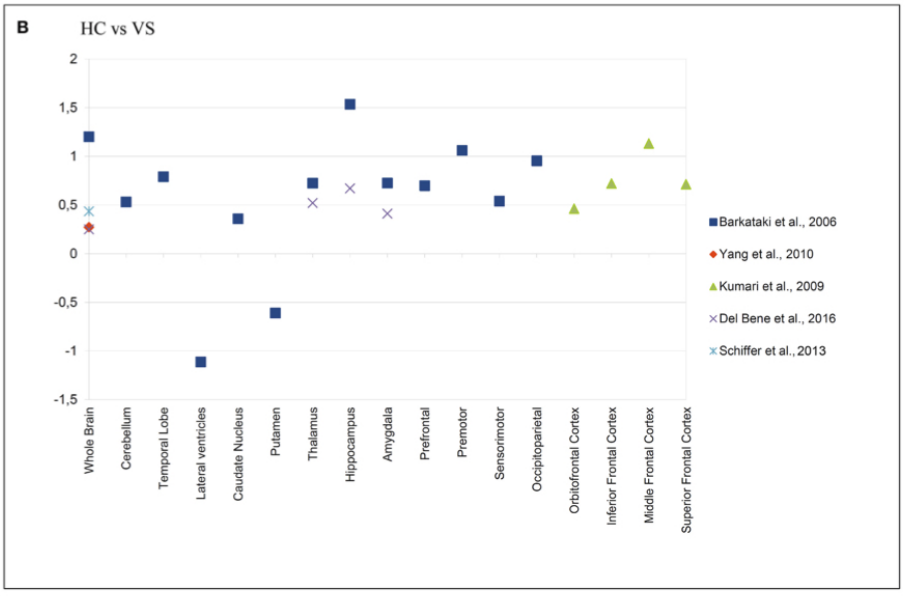


FIGURE 2 | (Continued)

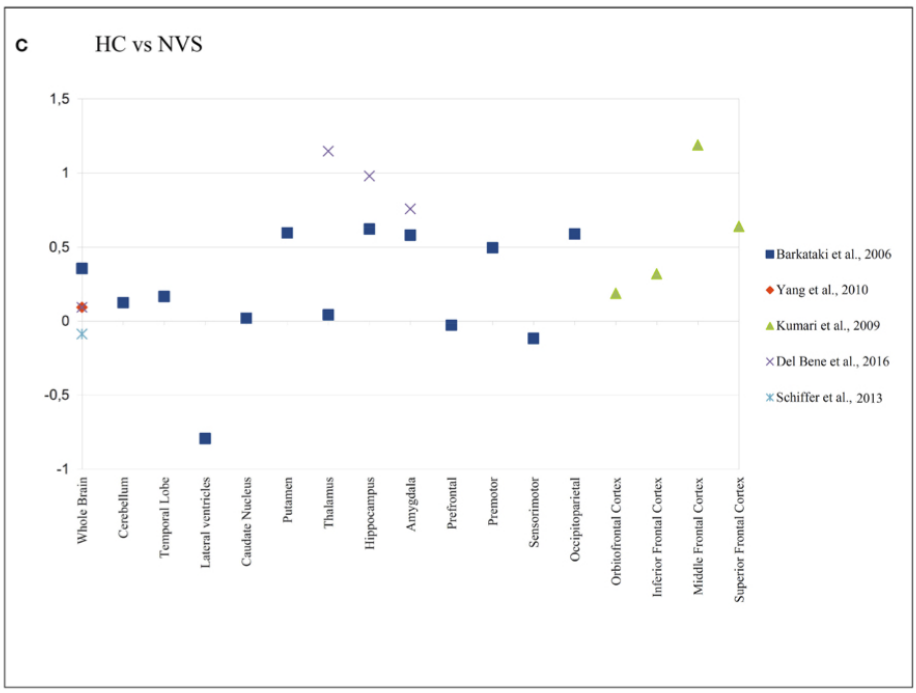


FIGURE 2 | Effect sizes of reported brain areas in different studies. **(A)** Group comparison of HC vs. NVS; **(B)** Group comparison of HC vs. VS; **(C)** Group comparison of VS vs. NVS. A positive value indicates that the first group has a greater volume than the second group in the comparison e.g., in **(A,B)**, the HC group, and in **(C)**, the VS group. HC, healthy controls; NVS, non-violent schizophrenia group; VS, violent schizophrenia group. Barkataki et al. (45), Del Bene et al. (53), Yang et al. (57) have used ROIs, while Kumari et al. (48), Kuroki et al (55), and Schiffer et al. (56) applied VBM.

TABLE 3 | Overview of the qualitative findings comparing volumes in violent vs. non-violent schizophrenia patients OR (in *italic*) of continuous measures of aggression in schizophrenia patients.

References	WB	Cer	TL	I	LV	CN	P	T	Hypo	Hip	Am	PFC	PMC	SMC	InfP	OPC	AC	OFC	InfF	MidF	SupF	PHG
Barkataki et al. (45)	↓	↓	↓		↑	↓	↑	↓		↓	↑	↓	↓	↓		↓						
Hoptman et al. (46)																		↑				
Hoptman et al. (52)						↑																
Narayan et al. (51)														↓								
Kumari et al. (48)			↓							↓	↑							↓	↓	↓	↓	
Kumari et al. (49)	↓		↓							↓	↑											
Kumari et al. (50)																	↔					
Puri et al. (54)	↓	↓																				
Yang et al. (57)	↓									↓												↓
Del Bene et al. (53)	↑							↑		↑	↑											
Kuroki et al. (55)	↓		↓	↓																		
Schiffer et al. (56)	↓						↑		↑						↑				↓			

WB, Whole Brain; Cer, Cerebellum; TL, Temporal Lobe; I, Insula; LV, Lateral Ventricles; CN, Caudate Nucleus; P, Putamen; T, Thalamus; Hypo, Hypothalamus; Hip, Hippocampus; Am, Amygdala; PFC, Prefrontal Cortex; PMC, Premotor Cortex; SMC, Sensorimotor Cortex; InfP, Inferior Parietal Cortex; OPC, Occipitoparietal Cortex; AC, Anterior Cingulate; OFC, Orbitofrontal Cortex; InfF, Inferior Frontal Cortex; MidF, Middle Frontal Cortex; SupF, Superior Frontal Cortex; PHG, Parahippocampal Gyrus. Articles marked blue used the same cohort, of which the work by Barkataki et al. (45) was the underlying primary study—The two studies by Hoptman et al. used the same cohort, as well (marked in italic). Red shading refers to relatively decreased volumes in violent schizophrenia vs. non-violent schizophrenia patients. Green shading refers to relatively increased volumes in violent schizophrenia vs. non-violent schizophrenia patients. Yellow shading refers to no significant differences in volumes between violent schizophrenia vs. non-violent schizophrenia patients.

Yang et al. (57) found reduced GM volume in the whole brain, hippocampus, and parahippocampal gyrus in VS compared with NVS. Puri et al. (54) reported that VS had smaller GM volume in the cerebellum than NVS and hypothesized that the cerebellum might be relevant for input from ventrolateral prefrontal cortex and parietal regions. Kuroki et al. (55) reported that VS as opposed to NVS showed significantly smaller volumes of the right inferior temporal area and the right insular area.

Schiffer et al. (56) observed that VS vs. NVS had increased volumes of the hypothalamus, left putamen, and right inferior parietal cortex. VS as opposed to NVS had smaller volumes of the inferior frontal region and also smaller whole brain volumes.

Del Bene et al. (53) reported larger whole brain volumes in VS as opposed to NVS. In the same group comparison, they found larger volumes in the amygdala, the hippocampus, and the thalamus.

In the group comparison of VS vs. NVS, we noted large negative effects on volume in the whole brain, temporal lobe, thalamus, hippocampus, prefrontal cortex, premotor cortex, sensorimotor cortex, and occipitoparietal cortex. In the same group comparison, we found large positive effects on volume in the amygdala (see **Figure 2A**).

Violent Persons With Schizophrenia vs. Healthy Controls

Kumari et al. (48) found significantly smaller PFC and hippocampal volume, and—at a trend level—smaller temporal lobe and amygdala volume in VS compared to HC. Kumari et al. (50) found significantly lower AC volumes in VS than in HC. When comparing HC vs. VS, we observed large positive effects on whole brain volume, cerebellum, temporal lobe, thalamus, hippocampus, amygdala, prefrontal cortex, premotor cortex, occipitoparietal cortex, and inferior, middle, and superior frontal cortex. In that group comparison, we found large negative effects in the LV and the putamen (see **Figure 2B**).

Non-violent Persons With Schizophrenia vs. Healthy Controls

NVS showed a trend for lower AC volumes than HC. The authors found no other significant group differences in volumes (50). Also, NVS showed smaller GM volume in prefrontal cortex than HC (57).

Kumari et al. (48) reported reduced PFC and amygdala volume in NVS compared to HC; furthermore, they observed that impulsiveness, as measured by the Impulsiveness-Venturesomeness-Empathy questionnaire [IVE-7, (58)], correlates negatively with reduced orbitofrontal GM volume. They hypothesized that dysfunctional, but not functional, impulsivity is elevated in repetitively violent persons with schizophrenia, and that this reduction in orbitofrontal GM may constitute a correlate of dysfunctional impulsivity.

When comparing HC vs. NVS we discovered large positive effects on volume in the putamen, hippocampus, amygdala, occipitoparietal cortex, middle frontal cortex, and superior frontal cortex. In the same group comparison, we found large negative effects in the LV (see **Figure 2C**).

Aggression Operationalized by Means of Questionnaires

Hoptman et al. (46, 52) used continuous measures to examine structural correlates of violence in schizophrenia in one subject population.

Hoptman et al. (46) found larger GM volumes in the left OFC to be associated with a higher degree of aggression as rated in the PANSS and Overt Aggression Scale (OAS). Also, larger GM volumes in the right OFC were associated with worse neuropsychological performance. The authors discussed the possibility that an increase in volume could constitute a correlate of reduced neural density, of increased neuronal size, of edema, or other pathophysiological processes. Hoptman et al. (52) reported that aggression in treatment-resistant schizophrenia or schizoaffective disorder is associated with a larger caudate volume.

In summary, studies measuring aggression by continuous means (using questionnaires) found increased volumes in the OFC as well as the caudate (46, 52) (see **Table 3**).

Effect Size Analysis

After excluding all studies with overlapping cohorts, insufficient data, or missing comparison group, four studies suitable for meta-analysis of effect size remained (see **Figure 1**). We calculated an effect size analysis over whole brain volumes as reported in the studies by Barkataki et al. (45), Del Bene et al. (53), Kuroki et al. (55), Schiffer et al. (56), and Yang et al. (56) (see **Table 4**).

We observed that HC showed larger whole brain volumes than persons with schizophrenia, independently of their history of violence. In addition, studies revealed that VS had smaller whole brain volumes than NVS.

DISCUSSION

With this systematic review and effect size analysis, we sought to compile all available data on structural MRI correlates of aggression, comparing persons with schizophrenia and healthy controls. This is the first systematic qualitative and quantitative review on this topic. To ensure high methodological quality, it was conducted according to the PRISMA guidelines and the revised QUORUM statements.

Qualitative Results

Non-violent Schizophrenia vs. Violent Schizophrenia

Volumes of whole brain, as well as cerebellum, temporal lobe, caudate nucleus, thalamus, hippocampus, prefrontal cortex, premotor cortex, sensorimotor cortex, occipitoparietal cortex, OFC, inferior, middle, and superior frontal cortex, and parahippocampal gyrus, are reported to be smaller in VS vs. NVS.

The parahippocampal gyrus volume reduction is specific to this group comparison. This structure is known to play an important role in scene recognition (59). This ability is reported to be impaired in violent persons (60) and also in persons with schizophrenia (61). Also, the parahippocampal gyrus seems to be involved in emotion processing (62). The authors, in a lesion study, detected that the structure may play a crucial role in

TABLE 4 | Effect size analysis of whole brain volume in HC vs. NVS and HC vs. VS as measured in the studies by Barkataki et al. (45), Del Bene et al. (53), Schiffer et al. (56), and Yang et al. (57).

	HC vs. NVS				HC vs. VS				NVS vs. VS			
	n	*Mean Effect Size*	*P p*	*Q*	*n*	*Mean Effect Size*	*p p*	*Q q*	*n*	*Mean Effect Size*	*p p*	*Q q*
Whole Brain	4	0.0356	0.8140	1.1197	4	0.4223	0.0042	4.0581	5	0.3555	0.0073	5.2540

In the group comparison NVS vs VS we could additionally include the study by Barkataki et al. (45), Del Bene et al. (53), Kuroki et al. (55), and Yang et al. (57) have used ROIs, while Kuroki et al. (55) and Schiffer et al. (56) applied VBM. n, number of studies; p, value of probability; Q, Homogeneity Coefficient.

comprehending social context (e.g., sarcasm). Poorer sarcasm comprehension was correlated with smaller parahippocampal gyrus volumes (62). An impaired comprehension of hidden meanings of communication in social contexts may lead to misunderstandings and, thus, may be connected with aggressive actions. Our finding is therefore compatible with the literature, while its specificity to aggression remains unclear.

The putamen, LV, and amygdala are reported to be larger in VS vs. NVS. The putamen is known to play a core role in regulating movement and learning abilities (63–65). Also, Zeki and Romaya (66) have reported the putamen to be hyperactivated when viewing a hated face vs. a neutral face. The increased putamen volumes in violent individuals may reflect an association with feeling hatred—still, antipsychotic pharmacotherapy is a potential moderator of this effect. In general, aggressive persons receive higher medication doses, and it is known that the intake of antipsychotic medication increases putamen volume (67, 68).

Amygdala volume has been reported to be reduced in aggressive or non-aggressive persons with schizophrenia as opposed to healthy controls. We find a larger amygdala volume in VS than in NVS. This finding is novel in the literature. The amygdala, as part of the limbic system, plays an important role in developing fear and in emotion regulation (69). A possible interpretation of our findings could be that the reductions in amygdala volumes are more pronounced in NVS than in VS, which could lead to the hypothesis that the amygdala is more prominent in aggression. Pardini et al. (70), in contrast, found lower amygdala volume to be associated with aggression.

There is no significant difference reported on anterior cingulate volume between VS and NVS.

Studies comparing persons with schizophrenia with higher or lower aggression scores in questionnaires found larger volumes in the caudate nucleus and in the OFC in persons with schizophrenia with higher aggression scores vs. those with lower aggression scores.

There are contradictory results concerning the OFC and caudate nucleus: Hoptman et al. (46) reported higher OFC volume while Kumari et al. (48) reported the OFC volume to be lower. Also, Hoptman et al. (52) found the caudate nucleus to be larger, while Barkataki et al. (45) reported this volume to be smaller. This difference may be attributable to the different study designs: both Hoptman papers examined aggression as a continuous measure while the reports by Barkataki and Kumari used categorical measures. Therefore, the contradictory findings could be attributed to the substantially different operationalization of aggression or potentially to medication effects.

Persons with schizophrenia independently of aggressive behavior show a general volume reduction in the whole brain and an increase in ventricular volumes. It remains unclear whether the differences in volumes described above are attributable to the aggressive behavior or to effects of disease or medication.

Healthy Controls vs. Violent Schizophrenia Persons

When comparing healthy controls with violent persons with schizophrenia, we found smaller volumes of the whole brain, cerebellum, temporal lobe, caudate nucleus, thalamus, hippocampus, amygdala, prefrontal cortex, premotor cortex, sensorimotor cortex, occipitoparietal cortex, OFC, and inferior, middle, and superior frontal cortices. In contrast, the putamen and LV were larger in violent persons with schizophrenia than in healthy controls.

Most of these differences equal those described for the comparison between healthy controls and non-violent persons with schizophrenia (17, 19, 20, 22, 39).

However, differences pertaining to the prefrontal cortex, sensorimotor cortex, and the putamen are specific to this group comparison.

We found the prefrontal cortex volume to be reduced in aggressive persons with schizophrenia. The prefrontal cortex is known to play an important role for the regulation of emotion (71, 72). We know emotional regulation to be impaired in aggressive persons (72). Our finding of reduced prefrontal cortex volume is therefore compatible with the current literature.

We found reduced sensorimotor cortex volume in violent persons with schizophrenia. This structure plays an important role in planning and executive motor functioning (73). We know that these abilities are impaired in persons with schizophrenia (74) and in aggression (75), and conclude that our finding of reduced sensorimotor cortex volume is also consistent with the literature.

We found increased putamen volume in violent persons with schizophrenia. As described above, the putamen volume increase plays an important role in feeling hatred, but might also be an effect of antipsychotic medication.

Healthy Controls vs. Non-violent Schizophrenia Persons

When comparing healthy controls with non-violent persons with schizophrenia we found smaller whole brain volume and smaller volumes of the cerebellum, temporal lobe, caudate

nucleus, putamen, thalamus, hippocampus, amygdala, premotor cortex, occipitoparietal cortex, OFC, and the inferior, middle, and superior frontal cortices in the schizophrenia group. Non-violent persons with schizophrenia had larger LV than the healthy controls. These findings are in line with the existing literature where Wright et al. (19) observed that the mean cerebral volume of persons with schizophrenia was smaller than in healthy controls, and that the total ventricular volume in persons with schizophrenia was enlarged in comparison to healthy participants. Shenton et al. (20) confirmed these findings by noting that persons with schizophrenia showed smaller WB volumes and enlarged ventricles. Also, they found amygdala, hippocampus, parahippocampal gyrus and neocortical temporal lobe regions to be smaller in persons with schizophrenia than in healthy controls. Fusar-Poli et al. (22) reported consistent GM reductions in temporal, anterior cingulate, cerebellar, and insular regions. In a meta-analysis, van Erp et al. (18) found smaller hippocampus, amygdala, thalamus, accumbens, and intracranial volumes, but larger lateral ventricles, in persons with schizophrenia as compared to healthy controls.

In the two comparisons of brain volume in VS and NVS as compared to HC, we consider the IQ score as a potential confounding factor. As IQ was significantly lower in the two patient groups as opposed to HC, this could further influence the reduced brain volumes in the patient groups. In a large-scale meta-analysis, McDaniel (76) reported a clear positive correlation between brain volume and intelligence.

Meta-Analytic Results

Violent persons with schizophrenia showed a significantly lower whole brain volume than healthy controls ($p = 0.0042$), and non-violent persons with schizophrenia had a significantly larger whole brain volume than violent persons with schizophrenia ($p = 0.0073$).

These findings could be influenced by factors related to aggression or further confounders (e.g., publication bias)—it could be possible, for example, that they are the effects of violent persons with schizophrenia receiving higher cumulative doses of antipsychotic or sedating medication, or of differences concerning co-morbid substance use disorder. Unfortunately, due to sample size restrictions and the failure of most studies to report potential confounding variables, this question cannot be further explored based on the available literature.

Non-violent persons with schizophrenia had a lower whole brain volume than healthy controls, although this difference is not significant. This finding is only partially in line with the literature: We would have expected a significantly smaller whole brain volume in both violent and non-violent persons with schizophrenia compared to healthy controls (19). However, non-significance in this case might be caused by the small sample size.

Challenges and Pitfalls

There are several major challenges when examining structural correlates of aggression in psychoses that limit the explanatory power of our systematic review and effect size analysis.

Operationalizing Aggression

Aggression in schizophrenia-spectrum disorders is difficult to examine due to the heterogeneous clinical picture of schizophrenia and the extensive variety of aggressive behaviors. In most of the reviewed articles, history of violence is not specified, and the scale of the violent acts remain unclear. This makes it impossible to control for the different types of aggression. Furthermore, from a clinical viewpoint, there are different trajectories of aggressive behavior (e.g., a number of minor aggressive events, one severe aggressive event, or a history of repeating aggressive events) that may be connected with different developmental pathways (e.g., repeated aggression in acute psychosis vs. development of a conduct or an antisocial personality disorder) and different neurobiological mechanisms of violence. Thus, further studies should aim to use narrow operationalizations of violence and to include more homogeneous patient populations to enable examination of these different pathways.

Predictors and Moderators of Aggression

There are many predictors of violent behavior (most importantly substance use disorder and antisocial personality disorder), however, the included studies do not sufficiently report information on these predictors nor do they systematically control for them. Therefore, we could not control for important moderators like psychopathology, general intelligence, or effect of medication. We recommend that future studies collect and report predictors of aggression in order to allow for moderator analyses. The most important factors that should be recorded and reported are antipsychotic medication, substance abuse comorbidities, IQ, and antisocial personality disorder.

Sample Size, Cohort Overlaps, Methodology, and Publication Bias

In general, small sample sizes and considerable cohort overlaps limit the interpretability of the current literature. Concerning the effect size analysis, the limited number of studies leads to a reduced statistical power, and results have to be considered preliminary and subjected to replication analyses when the situation of the published data has improved. Furthermore, according to Sterne et al. (77), the minimum number of studies needed for creating a funnel plot in meta-analyses is 10. Thus, due to sparse literature in the field, the important question of publication bias cannot be appropriately addressed yet. In addition, the use of different methods in measuring brain volumes (ROI-based analyses vs. VBM) complicate the interpretation of the findings. Although Focke et al. (78) indicated that both methods deliver comparable results, these methodological differences constitute an issue that has to be handled with caution. Replication studies will be needed in order to enable a better interpretation of the findings.

Affective Psychoses

With respect to our systematic literature search, there is no published literature on structural magnetic resonance correlates of aggression in affective psychoses. This is surprising since

persons with affective psychotic disorders are also at increased risk for aggressive behavior (4–6).

CONCLUSION

Violence in patients with psychosis is of high clinical and public relevance. We reviewed evidence for differences in brain volume correlates of aggression in persons with schizophrenia. However, due to considerable sample overlap in the literature and missing research on affective psychoses, further studies evaluating structural correlates of aggression in psychotic disorders are urgently needed. In order to enhance comparability of studies, we recommend that researchers adhere to clear and exact definitions of history of violence and report consistent measurements of psychopathology, including violence scores.

AUTHOR CONTRIBUTIONS

CH, SB, and RS designed the study. SW and HJ independently conducted literature search and data extraction, and CH supervised this process and helped reach a decision in case of disagreement. SW and JS analyzed the data. SW and CH wrote the initial draft of the paper. All authors contributed to data interpretation and manuscript preparation, and all authors read and approved the final version of the manuscript. SW and JS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00217/full#supplementary-material

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B Paper Two

Here, we display the paper: Widmayer, S., Borgwardt, S., Lang, U. E., Stieglitz, R.-D., & Huber, C. G. (2019). Functional Neuroimaging Correlates of Aggression in Psychosis: A Systematic Review with Recommendations for Future Research. *Frontiers in Psychiatry, 9*.

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SYSTEMATIC REVIEW
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Functional Neuroimaging Correlates of Aggression in Psychosis: A Systematic Review With Recommendations for Future Research

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Background and methods: Aggression in psychosis is clinically important. We systematically compiled the evidence on functional correlates of aggression in psychosis searching PubMed, EMBASE, ScienceDirect, and PsycINFO until September 2017. We included studies reporting functional brain imaging correlates of aggression comparing: (1) affective or non-affective psychosis groups with a history of violence or with aggression operationalized using questionnaires, (2) affective or non-affective psychosis groups with a history of violence or with aggression operationalized using questionnaires to controls, (3) affective or non-affective psychosis groups with a history of violence or with aggression operationalized using questionnaires to controls with diagnoses other than affective or non-affective psychoses. We applied no language restriction and required patients to have a DSM or ICD diagnosis of affective or non-affective psychosis.

Results: Our sample consisted of 12 studies with 334 patients and 113 controls. During n-back tasks, violent (VS) as opposed to non-violent persons with schizophrenia (NVS) hypoactivated their inferior parietal lobe. When anticipating shock, VS vs. NVS hyperactivated their medial prefrontal gyrus, cuneus, middle temporal gyrus, and middle occipital gyrus. When viewing negative emotional pictures, VS vs. NVS hyperactivated the middle frontal gyrus, inferior frontal gyrus, anterior cingulate, lingual gyrus, precentral gyrus, globus pallidus, mid-cingulate, and precuneus.

Limitations: Due to the small number of available studies, sample overlap, and insufficient reporting of relevant moderators we could not conduct a meta-analysis.

Conclusions: We found non-systematic functional correlates of aggression in schizophrenia. Only few studies using varied paradigms and often overlapping samples have been conducted. There have been no attempts to replicate any of the observed

findings in the published literature. Focusing on future directions, we recommend that authors adhere to clear definitions of aggression, measurements of psychopathology, comorbidities, and medication. In particular, replication studies would allow for a better synthesis of the findings.

PROSPERO Registration Number: CRD42016048579

Keywords: aggression, psychosis, schizophrenia, functional magnetic resonance imaging, systematic review

INTRODUCTION

Most persons with schizophrenia are not violent (1)– less than 10% of violent crimes in society is attributable to schizophrenia (2). According to Brekke et al. (3), persons with schizophrenia are at highly increased risks of becoming victims of violence.

Still, some of the patients suffering schizophrenia are at increased risks for aggressive behavior (4–6), even in the first episode of illness (7–10), and in at-risk mental states (11). This poses severe challenges to the patients themselves, their families and health care professionals. In this systematic review, we pooled the available evidence on functional neuroimaging correlates of aggression in psychosis—of which there is surprisingly little—to provide an overview on the biological underpinnings of this clinically important phenomenon and give advice for the future development of the field.

Functional Neuroimaging Findings in Aggression

Functional Neuroimaging Correlates of Aggression in Healthy Persons

Lotze et al. (12) found hyperactivated medial prefrontal cortices in healthy controls (HC) reacting aggressively in a game paradigm during fMRI. The dorsomedial PFC was hyperactivated when subjects selected the intensity of the aggressive response.

Pietrini et al. (13), in a PET study, found that HC hypoactivated their ventromedial prefrontal cortices in aggressive vs. neutral scenarios.

An important particularity implicated in aggression seems to be the hyperactivity of the limbic system in response to negative or provocative stimuli, particularly anger provoking stimuli (14).

Functional Neuroimaging Correlates of Aggression in Patient Populations

Persons with impulsive aggression and HC underwent fMRI while viewing emotional faces (15). Relative to controls, patients exhibited higher amygdala and lower orbitofrontal cortex (OFC) activation to angry faces. While HC did, aggressive subjects did not couple amygdala-OFC when seeing angry faces.

New et al. (16) provoked aggression in a laboratory setting with the Point Subtraction Aggression Paradigm. Patients with borderline personality disorder with an anger dyscontrol, as opposed to HC, showed hypoactivations to provocation in the medial frontal cortex and the anterior frontal cortex but hyperactivations in the orbital frontal cortex.

Preliminary Work on Functional Neuroimaging Correlates of Aggression in Psychosis

Some reviews have compiled data on functional neuroimaging correlates of aggression in psychoses.

Naudts and Hodgins (17) suggest that people with schizophrenia with as opposed to those without violent behavior perform better in executive function tasks and show less impairments in the dorsolateral prefrontal cortex. Hoptman and Antonius (18) sum up that frontal and temporal particularities seem to be a consistent feature of aggression in schizophrenia but that their nature remains unclear. Soyka (19) concludes that in schizophrenia patients with aggression as opposed to those without aggression certain brain functions may be more severely impaired.

Existing reviews have been conducted 6 years ago and are narrative expert reviews lacking systematic literature search and quantitative statistical measures. As to our knowledge, there are currently no studies reporting fMRI correlates of aggression in persons with affective psychoses.

Research Question

We aimed at conducting a systematic literature research and compiling all available data on functional neuroimaging correlates of aggression in patients with psychotic disorders: Are there systematic differences in the brain activation patterns in aggressive vs. non-aggressive persons with psychotic disorders? What recommendations for future research can be proposed based on the current state of the literature?

METHODS

We adopted the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines (20) and the revised "Quality of Reporting of Meta-analyses" QUORUM statements (21). The study protocol was registered on the International Prospective Register of Systematic Reviews database (PROSPERO; registration number: CRD42016048579) prior to the completion of data extraction. To assess the methodological quality of the current systematic review, we used the PRISMA 2009 checklist (20).

Search and Selection Strategy

We conducted a systematic review of fMRI studies on correlates of aggression in patients with psychoses vs. HC. We searched

the PubMed, EMBASE, ScienceDirect, and PsycINFO databases with no restriction on start date until September 2017. We used search thesauri representing aggression, psychosis and functional brain imaging. The detailed search terms can be found on http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016048579. Furthermore, we searched the reference lists of all included original articles for additional literature.

Subsequently, we screened all studies according to the following inclusion criteria. We included longitudinal, cross-sectional, and case-control studies (journal articles, book chapters, and dissertations) reporting brain imaging correlates of aggression comparing: (1) affective or non-affective psychosis groups with a history of violence or including continuous measures of aggression, (2) affective or non-affective psychosis groups with a history of violence or including continuous measures of aggression to HC, (3) affective or non-affective psychosis groups with a history of violence or including continuous measures of aggression to controls with diagnoses other than affective or non-affective psychoses. Furthermore, we included all studies with brain imaging using functional MRI and with an age of cases/controls of at least 18 years. We applied no language restriction and required patients to have an established diagnosis of affective or non-affective psychosis according to DSM or ICD.

If there was insufficient information to extract data, we contacted corresponding authors by email using coding sheets to collect study data. When we received no response from the authors, we contacted them again—then, if we received no response, we excluded the study.

Quality Assessment

The quality of the studies was assessed using an item-checklist constructed specifically for the current work and similar to the previously published quality assessment by Paulson and Bazemore (22). The recorded variables were assessed in terms of precision, directness and consistency of the data. The categories scored in the quality assessment are listed in **Supplementary Table 1** (0–2 points per item with a theoretical range of 0–38 for the total quality score). The included studies were rated according to the sum of the points and characterized as high quality (≥80% of the maximal sum of points), moderate-high (60–79%), moderate (40–59%), moderate-low (20–39%), and low quality studies (<20%). Six of the included studies had a high quality, four had a moderate-high quality, one had moderate quality, and one study moderate-low quality.

Data Extraction

The main outcome measures were the hyper- and hypoactivations in the specific brain regions of patient groups [violent persons with schizophrenia (VS) and non-violent persons with schizophrenia (NVS)] and HC. We extracted imaging center, name of the first author, year of publication, type of functional imaging analysis, population characteristics of HC and patient groups (group size, gender, age, IQ, violence score, psychopathology, medication), operationalization of aggression, stimulation material, sum of points in quality assessment of individual studies, and diagnosis from all studies.

Data Analysis

We performed a qualitative analysis of all included publications. Talairach coordinates were transformed into MNI coordinates using GingerALE software, version 2.3; available from http://brainmap.org/ale/ (23, 24). To provide a clearer overview on hyper- and hypoactivation patterns in the different tasks and groups over all papers using similar paradigms, we produced multislice activation pattern figures (**Figures 2–5**) in MRIcron (25) using the reported MNI coordinates for building three dimensional ROIs (version from 2nd of May 2016; available from http://people.cas.sc.edu/rorden/mricron/install.html).

RESULTS

Literature Search

The literature search identified 937 studies of interest. After screening and applying in- and exclusion criteria, 925 studies were excluded. Main reasons for these numerous exclusions were that included persons did not fulfill the relevant diagnostic criteria or that the paper did not examine correlates of aggression. The exact number of studies with specific reasons for exclusion are detailed in **Figure 1**.

Using the PRISMA template, we summarize the study selection procedure in **Figure 1**.

The final sample consisted of 12 studies with a total of 334 patients and 113 HC. After subtracting subject overlaps due to the publication of multiple papers using the same cohort, the sample consisted of 236 patients and 92 HC subjects. Barkataki et al. (26), Kumari et al. (27), and Kumari et al. (28) as well as both Wong et al. (29) and Wong et al. (30) used the same underlying patient population.

Diagnoses were either schizophrenia or schizoaffective disorder according to DSM-IV or ICD-10—no studies included affective psychoses.

Table 1 gives an overview of all included studies showing imaging center; name of the first author; year of publication; type of functional imaging analysis; population characteristics of HC, and patient groups (group size, gender, age, IQ, violence score, psychopathology, medication); operationalization of aggression; stimulation material; sum of points in quality assessment of individual studies; diagnosis.

Activation Patterns

Table 2 shows fMRI activation patterns across all tasks, brain areas, and group comparisons. For readers interested in more detail in the individual studies, the following sections summarize their results and provide tables about the specific areas and tasks involved. Bearing in mind **Table 2**, readers can choose to jump directly to the discussion section.

Working Memory

When operationalizing working memory functioning with Go/No-Go, VS vs. HC hypoactivated the right middle frontal gyrus, right posterior cingulate gyrus, and right superior

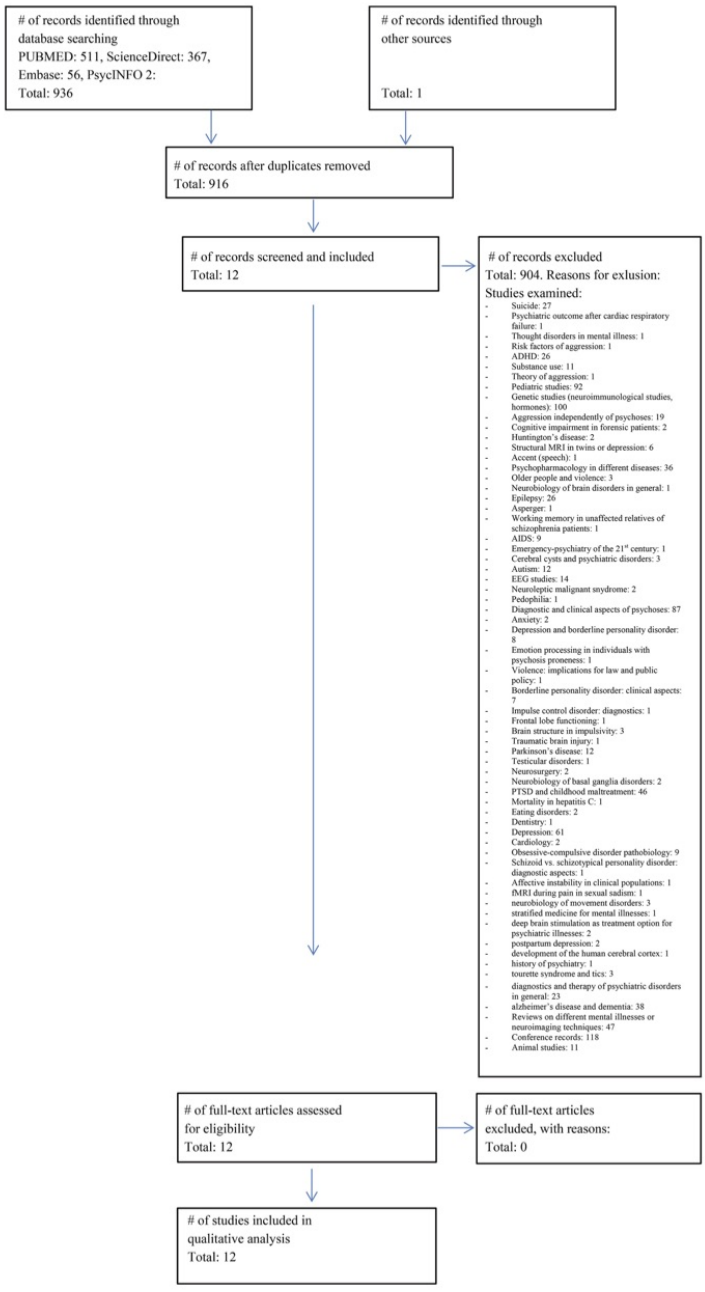


FIGURE 1 | Prisma flow chart. Flowchart of the literature search (03.09.2017) and included studies according to the PRISMA guidelines (20).

TABLE 1 | Overview of included studies.

Imaging center	First Author & Year of Publication	Type of fMRI analysis	HC: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD	NVS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	VS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	Operationalization of Aggression	Stimulation Material	Sum of Points in Quality assessment of individual studies (Maximum points: 38)	Diagnosis
UK: Institute of Psychiatry and Maudsley Hospital, London and Broadmoor Special Hospital, Berkshire	Barkataki et al., 2008	SPM99	14 14/0 32.1/7.8 WAIS IQ: 104.6/15.1 Gunn & Robertson score: 0.5/0.8	12 12/0 34.9/7.6 WAIS IQ: 87.9/13.4 Gunn & Robertson score: 1.5/1.3 PANSS total score: 63.1/10.9 533.7/354.1	12 12/0 34.8/4.9 WAIS IQ: 82.9/9.9 Gunn & Robertson score: 6.3/1.5 PANSS total score: 53.9/13.1 429.1/288.4	History of Violence	Go-NoGo	31	DSM-IV SCID: Schizophrenia
	Kumari et al., 2006	SPM99	13 13/0 33.3/6.8 NART IQ: 107.5/17.2 Gunn & Robertson score: 0.5/0.9	13 13/0 33.8/7.6 NART IQ: 101.1/12.2 Gunn & Robertson score: 1.2/1.3 PANSS positive symptoms: 12.3/4.1 PANSS negative symptoms: 19.2/4.9 PANSS general psychopathology: 32.9/5.9 Not reported	12 12/0 34.0/4.86 NART IQ: 95.7/14.3 Gunn & Robertson score: 6.0/1.4 PANSS positive symptoms: 9.7/2.9 PANSS negative symptoms: 17.0/4.5 PANSS general psychopathology: 22.4/2.9 Not reported	History of Violence	*n*-back task modified version: monitoring of locations of dots within a diamond shaped box on the screen 3 conditions: 0-, 1-, 2- back	33	DSM-IV SCID: Schizophrenia: paranoid, undifferentiated, residual, disorganized subtypes
	Kumari et al., 2009	SPM2	14 14/0 33.1/8.6 NART IQ: 107.4/16.5 Gunn & Robertson score: 0.5/0.9	13 13/0 34.3/7.3 NART IQ: 98.8/14.4 Gunn & Robertson score: 1.4/1.3 PANSS positive symptoms: 12.4/4.1 PANSS negative symptoms: 20.2/5.7 PANSS general psychopathology: 33.7/5.6 567/323.5	13 13/0 34.5/4.9 NART IQ: 96.4/13.9 Gunn & Robertson score: 6.1/1.5 PANSS positive symptoms: 11.0/5.6 PANSS negative symptoms:18.2/5.7 PANSS general psychopathology: 25.4/6.02 426.7/227.6	History of Violence In VS group: 5 homicide 2 attempted murder 4 wounding 2 interpersonal violence	Anticipation of electric shock	33	DSM-IV SCID: Schizophrenia: paranoid, undifferentiated, disorganized, and residual subtypes

(Continued)

TABLE 1 | Continued

Imaging center	First Author & Year of Publication	Type of fMRI analysis	HC: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD	NVS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	VS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	Operationalization of Aggression	Stimulation Material	Sum of Points in Quality assessment of individual studies (Maximum points: 38)	Diagnosis
Centre for Forensic Behavioral Science, Monash University and the Victorian Institute for Forensic Medical Health, Victoria, Australia	Dolan and Fullam, 2009	SPM5	No HC group	Schizophrenia persons with history of violence: 24 24/0 36.3/9.2 NART IQ: 102.6/10.7 WAIS IQ: 87.75/18.0 Not reported PANSS total score: 47.7/12.5 563.1/429.6 Psychopathy: 12-item Psychopathy Checklist: Screening Version (PCL:SV). Median of total psychopathy score (12.5) was used to split the sample into high and low psychopathy groups Low psychopathy: $n = 12$, high psychopathy: $n = 12$. Low psychopathy 12 12/0 40.7/10.4 NART IQ: 100.5/9.9 WAIS IQ: 92.5/17.6 Not reported PANSS total score: 46.9/11.7 565.8/366.1	High psychopathy 12 12/0 35.9/7.6 NART IQ: 104.6/11.5 WAIS IQ: 83.0/17.9 Not reported PANSS total score: 48.4/13.7 560.4/465.6	History of violence: 2 arson with intent to cause injury, 11 actual/grievous bodily harm, 2 violent sexual offenders, 2 attempted murder, 7 manslaughter/murder	Exposure to negative emotions in faces: Face expression recognition task (pictures of facial affect series): anger, disgust, fear, sad	30	DSM-IV SCID: Schizophrenia
Centro de Investigación Biomédica en Red en Salud Mental, Valencia, España	Garcia-Marti et al., 2013	SPM8	No HC group, only persons with schizophrenia, all of which have a certain history of violence, divided into three groups: low, middle and high aggression groups. Total sample: 32 32/0 40.9/9.8 Global Assessment of Functioning GAF BPRS: "hostility" item for aggression			BPRS Only patients with some aggressive behavior (not "1" in BPRS)	Verbal auditive stimulation with emotional content: 6 words with imperatives, 3 insults, 2 exclamations, 2 positive words	16	DSM-IV SCID: Schizophrenia

(Continued)

TABLE 1 | Continued

Imaging center	First Author & Year of Publication	Type of fMRI analysis	HC: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD	NVS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	VS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	Operationalization of Aggression	Stimulation Material	Sum of Points in Quality assessment of individual studies (Maximum points: 38)	Diagnosis
			Low aggression group: grade 2 & 3 of BPRS 12 12/0 39.7/8.9 GAF: 42.7/9.2 BPRS: 49.9/9.1 Psychotic Symptom Rating Scale PSYRATS: 39.1/11.7	Middle aggression group: grade 4 & 5 of BPRS 11 11/0 42.7/8.5 GAF: 35.7/11.0 BPRS: 55.8/8.2 PSYRATS:41.5/10.2	High aggression group: grade 6 & 7 of BPRS 9 9/0 39.8/8.1 GAF: 33.7/10.8 BPRS: 63.3/8.5 PSYRATS: 40.5/11.9				
USA: Nathan Kline Institute at Rockland Psychiatric Center, Orangeburg, NY Dorothea Dix Hospital, North Carolina	Hoptman et al., 2009	FSL	21 16/5 40.4/10.8 WAIS IQ: 105.5/12.1 BPAQ total score: 50.8/12.5 LHA total score: 10.2/5.3	25 patients 22/3 36.7/10.5 WAIS IQ: 94.3/13.5 BPAQ total score: 61.1/17.4 LHA total score: 14.2/10.3 PANSS total: 78.7/16.0 1157.8/627.2		Buss Perry Aggression Questionnaire total score: BPAQ	Resting state fMRI: closed eyes and awake	29	DSM-IV SCID: Schizophrenia ($n = 21$) or schizoaffective disorder ($n = 4$) Schizophrenia subtypes: 1 disorganized, 7 paranoid, 3 residual, 10 undifferentiated
Department of Forensic Psychiatry, University of Kuopio, Niuvanniemi Hospital, Finland	Joyal et al., 2007	SPM2	12 12/0	0	12 12/0	History of Violence	Go-NoGo	25	DSM-IV SCID: Schizophrenia, paranoid subtype
Department of Psychiatry, University of Rome Tor Vergata, Rome, Italy	Spalletta et al., 2001	Not reported	0	15: 3 "aggressive," 12 "not aggressive". No further sample informations		"behavior of the patient during the first week of hospitalization and was derived from the recordings of the entire clinical staff"	SPECT: closed eyes and awake AND Wisconsin Card Sorting Test	13	DSM-IV SCID: Schizophrenia

(Continued)

TABLE 1 | Continued

Imaging center	First Author & Year of Publication	Type of fMRI analysis	HC: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD	N/S Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	VS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	Operationalization of Aggression	Stimulation Material	Sum of Points in Quality assessment of individual studies (Maximum points: 38)	Diagnosis
Division of Forensic Psychiatry, Department of Psychiatry, Psychotherapy and Preventive Medicine, University Hospital, RUhr-University Bochum, Bochum, Germany	Schiffer et al., 2017	SPM8	18 18/0 36.3/9.8 11.1/11 Number of criminal convictions: 0/0	18 18/0 37.8/8.3 Premorbid IQ: 102/10 Number of criminal convictions: 0/0 PCL:SV total score: 3.3/1.6 PANSS positive symptoms: 7.3/3.0 negative symptoms: 19.8/3.7 cognitive syndrome: 8.2/3.0 hostile excitement: 9.7/2.4 depression: 6.6/1.3 633/395	16 16/0 38.4/9.0 Premorbid IQ: 107/14 Number of criminal convictions: 1.8/1.8 PCL:SV total score: 5.8/2.6 PANSS positive symptoms: 7.0/3.6 negative symptoms: 17.4/5.8 cognitive syndrome: 7.2/2.5 hostile excitement: 12.4/3.1 depression: 9.4/3.7 599/393	History of Violence	Simplified version of the "Reading-the-Mind-in-the-Eyes" task (RMET) involving mental state decoding from visual stimuli	32	DSM-IV: schizophrenia
Centre de recherche de l'Institut Universitaire en Santé Mentale de Montréal, Department of Psychiatry, University of Montreal, Canada	Tikàsz et al., 2016	Brain Voyager QX	21 21/0 30.3/11.7 Never lower than 70 Not reported	19 19/0 31.4/11.7 Never lower than 70 Not reported PANSS positive symptoms: 12.1/0.8 negative symptoms: 15.5/1.3 disorganization: 8.5/0.4 excitation: 7.5/0.6 depression: 7.1/0.4 654.4/74.7	20 20/0 30.0/11.6 Never lower than 70 Not reported PANSS positive symptoms: 9.1/2.4 negative symptoms: 12.9/5.5 disorganization: 6.8/1.9 excitation: 8.3/3.0 depression: 6.5/2.3 846.9/170.7	History of Aggression	View blocks of emotionally positive, negative & neutral pictures from the International Affective Picture System (IAPS) 5 experimental conditions: High arousal/positive, high arousal/negative, low arousal/positive, low arousal/negative, neutral	34	DSM-IV SCID: Schizophrenia or schizoaffective disorder

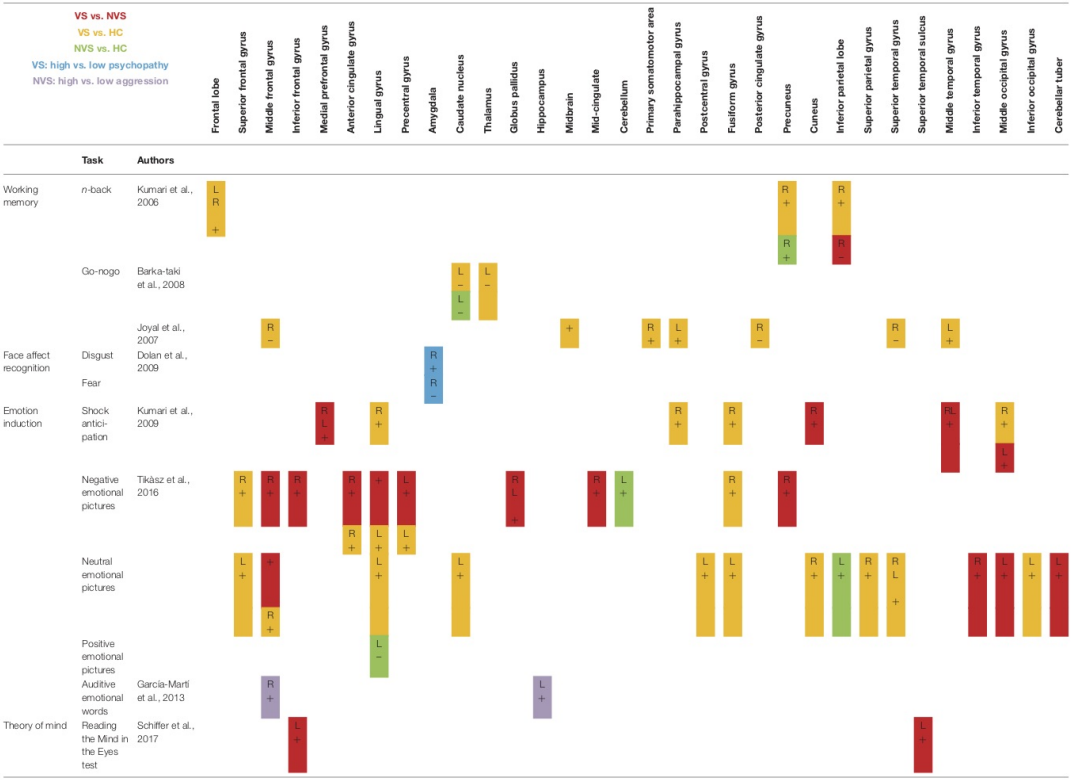
(*Continued*)

TABLE 1 | Continued

Imaging center	First Author & Year of Publication	Type of fMRI analysis	HC: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD	NVS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	VS Patients: N m/f Age: mean/SD IQ: mean/SD Violence Score: mean/SD Psychopathology: mean/SD Medication: mean/SD [chlorpromazine equivalents mg/d]	Operationalization of Aggression	Stimulation Material	Sum of Points in Quality assessment of individual studies (Maximum points: 38)	Diagnosis
Guy's and St. Thomas's Clinical PET centre, Knoxville, TN, USA	Wong et al., 1997	Not reported	6 6/0 35.2/9.6 Not reported Not reported	0	17 Repetitive violent offenders 17/0 36.2/6.8 Not reported Not reported Not reported 14 Non-repetitive violent offenders 14/0 40.4/10.1 Not reported Not reported Not reported	Repetitive or non-repetitive violent offending	–	26	26 DSM-IV SCID: Schizophrenia or schizoaffective disorder
	Wong et al., 1997	Not reported	Nothing reported, except that there have been healthy controls	0	20 Repetitive violent offenders 20/0 37.7/8.5 WAIS IQ: 91/12 Not reported Not reported 575/768.8 19 Non-repetitive violent offenders 19/0 40.4/10.6 WAIS IQ: 93/18 Not reported Not reported 1370.3/1202.2	Repetitive or non-repetitive violent offending	–	26	26 DSM-IV SCID: Schizophrenia or schizoaffective disorder

Overview of the studies included in the qualitative report describing imaging center; name of the first author; year of publication; type of imaging analysis; population characteristics of healthy controls and patient groups; operationalization of aggression; stimulation material; quality score; diagnosis. HC ≙ healthy controls, NVS ≙ non-violent schizophrenia group, VS ≙ violent schizophrenia group, HoV ≙ History of Violence, PANSS ≙ Positive and Negative Syndrome Scale, NART IQ ≙ National Adult Reading Test for estimating premorbid intelligence levels, WAIS IQ ≙ Wechsler Adult Intelligence Scale to measure cognitive ability in adults, Gunn & Robertson Scale ≙ 5-item scale for rating violence and other criminal activities, DSM-IV ≙ Diagnostic and Statistical Manual of Mental Disorders, fourth edition, SCID ≙ Structured Clinical Interview for DSM disorders.

TABLE 2 | Activation pattern overview.



Activation patterns in different tasks over all studies. +, Hyperactivation; –, Hypoactivation; L, left; R, right.

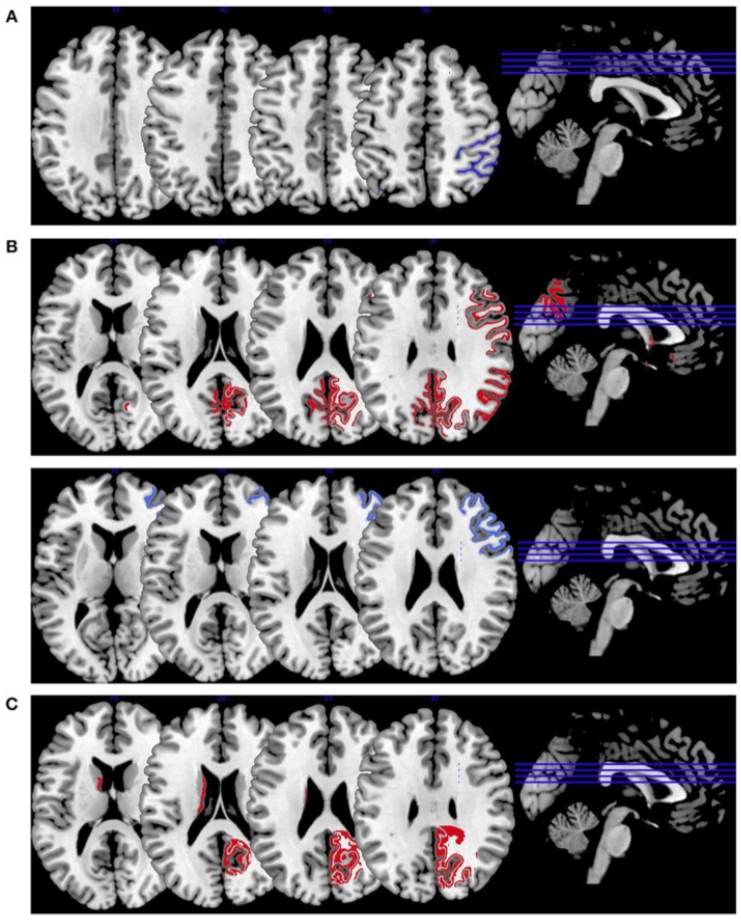


FIGURE 2 | Working memory activations. Overview of the working memory brain activation patterns reported by the reviewed studies. Hyperactivations are shown in red, hypoactivations in blue. **(A)** shows the activation patterns in the group comparison VS vs. NVS with VS<NVS in blue (shown slice numbers are 210, 220, 230, 240) in the contrast 2-back vs. 0-back, **(B)** shows the activation patterns in the group comparison VS vs. HC with VS>HC in red (shown slice numbers are 170, 180, 190, 200) in the contrasts 1- and 2-back vs. 0-back and cognitive (go/no-go task) vs. reference condition and VS<HC in blue (shown slice numbers are 160, 170, 180, 190) in the contrast NoGo20 vs. NoGo40 and NoGo40 vs. Go and cognitive (go/no-go task) vs. reference condition, **(C)** shows the activation patterns in the group comparison NVS vs. HC with NVS>HC in red (shown slice numbers are 170, 180, 190, 200) in the contrast 1- and 2-back vs. 0-back.

temporal gyrus (31). In contrast, VS as opposed to HC hyperactivated the left middle temporal gyrus, midbrain, right primary somatomotor area, left parahippocampal gyrus (31) and hypoactivated the left thalamus and left caudate nucleus (26). NVS as opposed to HC hypoactivated solely the left caudate nucleus.

Working memory as measured by the n-back task showed that VS vs. HC hyperactivated the frontal lobe bilaterally, the right precuneus, and the right inferior parietal lobe. NVS vs. HC hyperactivated the right precuneus, while VS vs. NVS hypoactivated the right inferior parietal lobe (27). **Table 3** shows an overview.

Face Affect Recognition

Dolan and Fullam (32) compared VS with high vs. low psychopathy using a face affect recognition task. When viewing a disgustful face, high psychopathy VS hyperactivated the right amygdala—when viewing a fearful face, they hypoactivated it (see **Table 4**).

Emotion Induction

Shock Anticipation

Kumari et al. (28) conducted a fMRI study where participants (VS, NVS and HC) were threatened to receive an electric shock. Under shock anticipation, VS as opposed to HC hyperactivated

TABLE 3 | Activation patterns in working memory.

Group comparison		Working memory																
		Go-NoGo											*n*-back					
VS vs. HC	Region	MFG		MTG	Midbrain	PSMA	PHG	T	CN	PCG	STG		FL		P		IPL	
	H	R		L	R	R	L	L	L	R	R		L & R		R		R	
	V	33		17	86	133	16	33	758	55	53		260		611		446	
													226		1,147			
													209					
													325					
	Coordinates (x, y, z)	55.28, 39.45, 19.7		−35, −2.64, −35.1	1.01, −31.59, −13.8	68.55, −2.01, 34.79	−18.62, 1.96, −21.27	−5.15, −29.23, 11.84	−18, −23.98, 22.75	17.8, −60.01, 25.7	55.21, −5.93, 5.14		−30, 8, 50		6, −62, 46		46, −50, 48	
													40, 6, 46		46			
													−30, 10, 48		6, −61, 48			
													28, 14, 48					
	p	0.048		0.002	0.002	0.006	0.007	<0.001	0.017	0.002	0.002		0.001		0.001		0.001	
NVS vs. HC	Region	Caudate Nucleus											Precuneus					
	H	L											R					
	V	860											430					
													638					
	Coordinates (x, y, z)	−18, −23.98, 22.75											10, −58, 48					
													6, −60, 48					
	p	0.011													0.001			
VS vs. NVS	Region												Inferior Parietal Lobe					
	H												R					
	V												60					
	Coordinates (x, y, z)												54, −48, 46					
	p														0.001			

Hyperactivations and *Hypoactivations*. *H ≙ Hemisphere, V ≙ Cluster Size in Voxels, Coordinates ? MNI. MFG ≙ Middle Frontal Gyrus, MTG ≙ Middle Temporal Gyrus, PSMA ≙Primary Somatomotor Area, PHG ≙ Parahippocampal Gyrus, T ≙ Thalamus, CN ≙ Caudate Nucleus, PCG ≙ Posterior Cingulate Gyrus, STG ≙ Superior Temporal Gyrus, FL ≙ Frontal Lobe, P ≙ Precuneus, IPL ≙ Inferior Parietal Lobe. Black box ≙ Results reported by Barkataki et al. (26), green box ≙ results reported by Kumari et al. (27). Results without box are reported by Joyal et al. (31).*

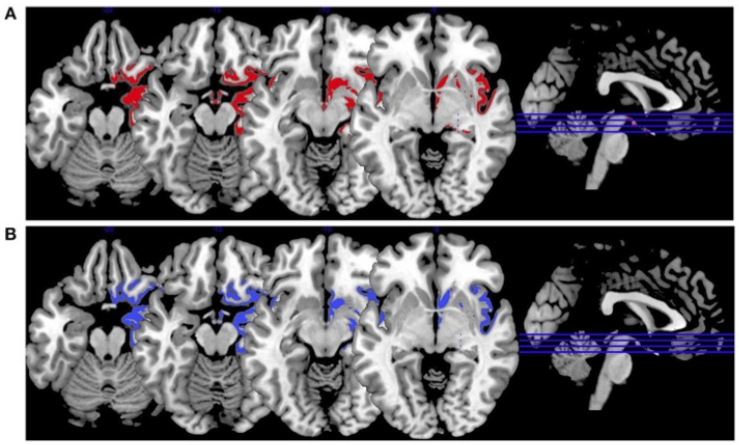


FIGURE 3 | Face affect recognition activations. Overview of the working memory brain activation patterns reported by the reviewed studies in the group comparison VS high vs. VS low. Hyperactivations are shown in red, hypoactivations in blue. **(A)** Shows the activation patterns in the group comparison VS high vs. VS low with VS high>VS low in red showing the contrast of neutral vs. disgustful faces, **(B)** shows the activation patterns in the group comparison VS high vs. VS low with VS high<VS low in blue showing the contrast of neutral vs. fearful faces. Shown slice numbers are 100, 110, 120, 130.

TABLE 4 | Activation patterns in face affect recognition.

Group comparison		Face affect recognition	
		Disgust	Fear
VS: high vs. low psychopathy	Region	Amygdala	Amygdala
	H	R	R
	V	3	2
	Coordinates (x, y, z)	28, −4, −21	25, 0, −21
	p	0.026	0.026

Hyperactivations and Hypoactivations as reported by (33). H ≙ Hemisphere, V ≙ Cluster Size in Voxels, Coordinates ≙ MNI.

the right fusiform/inferior temporal gyrus as well as the right lingual/posterior cingulate gyrus.

VS vs. NVS hyperactivated the medial prefrontal/cingulate gyrus bilaterally, middle temporal gyrus bilaterally, right posterior cingulate/cuneus, and left middle occipital gyrus (see **Table 5A**).

Emotional Pictures

Tikàsz et al. (34) showed negative emotional pictures to VS, NVS, and HC and observed functional alterations in brain activity (see **Table 5B**).

VS vs. HC hyperactivated the right fusiform gyrus, right superior frontal gyrus, right anterior cingulate, left lingual gyrus, and left precentral gyrus.

NVS vs. HC hyperactivated the superior temporal gyrus bilaterally, left cerebellum, left posterior cingulate gyrus, left hippocampus, and left inferior parietal lobe.

VS vs. NVS hyperactivated right anterior cingulate, right lingual gyrus, left precentral gyrus, right middle frontal gyrus, right inferior frontal gyrus, and superior temporal gyrus, globus pallidus bilaterally, right precuneus, and right mid-cingulate.

Tikàsz et al. (34) showed also positive and neutral emotional pictures to their participants (see **Table 5C**).

When viewing positive pictures, NVS vs. HC hypoactivated the left lingual gyrus.

VS vs. HC showed significant hyperactivations in response to neutral pictures in right middle frontal gyrus, right superior temporal gyrus, right superior parietal gyrus, right cuneus, left caudate nucleus, left superior frontal gyrus, left postcentral gyrus, left lingual gyrus, left inferior occipital gyrus, and left fusiform gyrus. NVS vs. HC hyperactivated the left inferior parietal gyrus.VS vs. NVS, when viewing neutral pictures, hyperactivated right middle frontal gyrus, right inferior temporal gyrus, left middle occipital gyrus, and left cerebellar tuber.

Emotional Words

García-Martí et al. (35) stimulated their subjects with auditive emotional words. In this paradigm, NVS with high aggression scores as opposed to those with low aggression scores hyperactivated the left hippocampus and the right medial frontal cortex (see **Table 5D**).

Affective Theory of Mind

Schiffer et al. (36) showed a picture of a person's eyes to their participants and let them select—out of two words—the one that fitted best the person's emotional state. They found that, when performing this task, VS as compared to NVS hypoactivated the left ventrolateral PFC and left superior temporal sulcus at the temporoparietal junction (see **Table 6**).

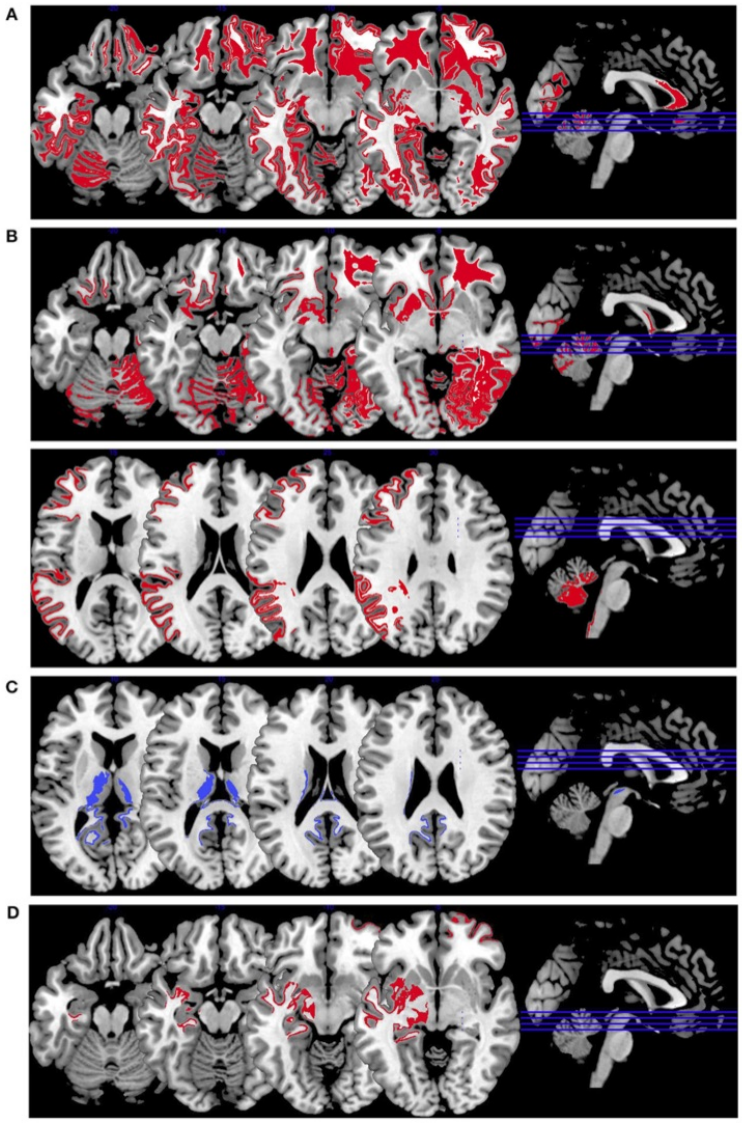


FIGURE 4 | Emotion induction activations. Overview of the working memory brain activation patterns reported by the reviewed studies. Hyperactivations are shown in red, hypoactivations in blue. **(A)** shows the activation patterns in the group comparison VS vs. NVS with VS>NVS in red (shown slice numbers are 100, 110, 120, 130) in the contrasts shock anticipation phase II (last 21 s after threatening with an electric shock) vs. shock anticipation phase I (first 9 s after threat) and negative vs. neutral emotional pictures and neutral emotional pictures vs. rest, **(B)** shows the activation patterns in the group comparison VS vs. HC with VS>HC in red (shown slice numbers are 100, 110, 120, 130) in the contrasts shock anticipation vs. safe condition and in negative vs. neutral emotional pictures contrast and neutral emotional pictures vs. rest, **(C)** shows the activation patterns in the group comparison NVS vs. HC with NVS>HC in red (shown slice numbers are 170, 180, 190, 200) in the contrast negative vs. neutral emotional pictures and NVS<HC in blue (shown slice numbers are 160, 170, 180, 190) in the contrast positive vs. neutral emotional pictures, **(D)** shows the activation patterns in the group comparison NVS high vs. low aggression with NVS high>NVS low in red (shown slice numbers are 100, 110, 120, 130) in the contrast of hearing emotional words (positive and negative ones) vs. rest.

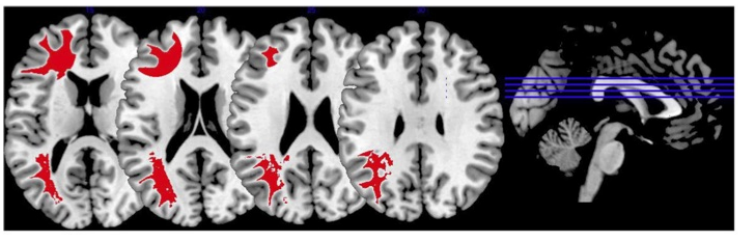


FIGURE 5 | Affective theory of mind activations. Overview of the affective theory of mind brain activation patterns reported by the reviewed studies, the group comparison being VS vs. NVS in the contrast of mental state attribution vs. gender discrimination. Here, we show the hyperactivation of VS>NVS in red (shown slice numbers are 170, 180, 190, 200).

TABLE 5A | Activation patterns in emotion induction: shock anticipation.

Group comparison		Emotion induction				
		Shock anticipation				
VS vs. HC	Region	FITG	LPCG			
	H	R	R			
	V	1,168	4,527			
	Coordinates (x, y, z)	42, −52, −16 28, −44, −6 30, −58, −12	24, −66, 2 28, −58, −2 26, −74, 20			
	p	0.031	<0.001			
VS vs. NVS	Region			MPCG	MTG	PCC	MOG
	H			R L L	R L	R	L
	V			2,176	4,008 1,155	Not reported	1,256
	Coordinates (x, y, z)			20, 32, −14 −6, 24, −2 −16, 26, −8	42, −60, 16 50, −12, −2 −44, −34, −14 −36, −26, −6	26, −74, 14	−28, −84, 10 −32, −76, 24 −20, −66, 6
	p			<0.001	<0.001 0.016	Not reported	0.01

Hyperactivations and Hypoactivations as reported by Kumari et al. (28). H ≙ Hemisphere, V ≙ Cluster Size in Voxels, Coordinates ≙ MNI. FITG ≙ Fusiform/Inferior Temporal Gyrus, LPCG ≙ Lingual/Posterior Cingulate Gyrus, MPCG ≙ Medial Prefrontal/Cingulate Gyrus, MTG ≙ Middle Temporal Gyrus, PCC ≙ Posterior Cingulate/Cuneus, MOG ≙ Middle Occipital Gyrus.

Activation Patterns as Described by Other Studies

Hoptman et al. (37) conducted a resting-state fMRI study to examine amygdala/ventral prefrontal cortex connectivity in aggression and schizophrenia with HC and patients with schizophrenia and schizoaffective disorder. Lower functional connectivity between amygdala and ventral PFC was associated with higher levels of self-rated aggression, life history of aggression and total arrests leading to the hypothesis that amygdala and ventral PFC functional connectivity may be compromised in aggressive schizophrenia (37).

Spalletta et al. (38) assessed the relationship between prefrontal function and aggression in schizophrenia using single photon emission tomography and evaluated patients at rest and during activation with the Wisconsin Card Sorting Test (WCST). Clinical staff recorded aggression ratings. Aggressive and non-aggressive patients did not differ in RCBF during rest. During WCST activation, aggressive vs. non-aggressive subjects hypoactivated the right middle and inferior PFC. The authors

TABLE 5B | Activation patterns in emotion induction: negative emotional pictures.

Group comparison	Emotion induction																													
	Negative emotional pictures																													
VS vs. HC	Region	FG		SFG	AC	LG	PG		STG		C		PCG		H		IPL													
	H	R		R	R	L	L		R	L	L		L		L		L													
	V	12,498		362	1,031	1,852	1,389		402 765		1,619		6,264		1,905		2,579													
	Coordinates (x, y, z)	40.12, −76.88, −6.63		17.64, 46.08, 35.38	40.15, 48.68, 4.99	−18.32, −84.4, −14.97	−40.62, 3.78, 33.83		36.22, 16.55, −39.35	−50.3, −51.75, 26.04	−5.86, −42.18, −46.26	−31.7, −54.72, −41.21	−1.87, −36.56, 13.63		−34.6, −32.47, −9.75		−43.48, −49.23, 52.57													
	p	<0.001		<0.001	<0.001	<0.001	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001													
NVS vs. HC	Region																													
	H																													
	V																													
	Coordinates (x, y, z)																													
	p																													
VS vs. NVS	Region				AC	LG	PG											MFG		IFG/STG		GP		P		MC			
	H				R	R	L											R		R		R	L	R		R			
	V				2,159	98,791	1,828											1,217		903		1,027	2,052	728		1,027			
	Coordinates (x, y, z)				4.1, 41.68, −11.02	1.36, −89.15, 1.97	−43.89, 0.26, 30.87											36.61, 58.99, 0.16		36.51, 8.95, 18.42		26.92, −16.3, 12.4	−21.67, −12.97, −8.54	24.54, −72.26, 43.61		4.73, 0.43, 30.03			
	p				<0.001	<0.001	<0.001											<0.001		<0.001		<0.001		<0.001		<0.001			

Negative Emotional Pictures. Hyperactivations and Hypoactivations as reported by Tikácz et al. (34). *H* ≙ *Hemisphere, V* ≙ *Cluster Size in Voxels, Coordinates* ≙ *MNI. FG* ≙ *Fusiform Gyrus, SFG* ≙ *Superior Frontal Gyrus, AC* ≙ *Anterior Cingulate, LG* ≙ *Lingual Gyrus, PG* ≙ *Precentral Gyrus, STG* ≙ *Superior Temporal Gyrus, C* ≙ *Cerebellum, PCG* ≙ *Posterior Cingulate Gyrus, H* ≙ *Hippocampus, IPL* ≙ *Inferior Parietal Lobe, MFG* ≙ *Middle Frontal Gyrus, IFG/STG* ≙ *Inferior Frontal Gyrus/Superior Temporal Gyrus, GP* ≙ *Globus Pallidus, P* ≙ *Precuneus, MC* ≙ *Mid-Cingulate.*

TABLE 5C | Activation patterns in emotion induction: positive and neutral emotional pictures.

Group comparison		Emotion induction																	
		Positive emotional pictures						Neutral emotional pictures											
VS vs. HC	Region	MFG	STG	SPG	C	CN	SFG	PG	LG	IOG	FG	IPG	ITG	MOG	CT				
	H	R	R L	R	R	L	L	L	L	L	L								
	V	15.541	904 1,393	2.987	1,080	5.679	1.209	14.975	1,031	8.061	408								
	Coordinates (x, y, z)	66.33, 17.23, 34.04	46.02, 17.31, −32.86 −41.39, 4.55, −26.74	34.31−52.15, 51.54	24.32, −93.59, 22.19	−15.26, 19.27, −8.47	−2.06, 67.1, 20.19	−49.97, −26.3, 57.14	−11.87, 87.88, −18.1	−50.55, −86.46, −0.77	−24.85, 71.66, −16.12								
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001								
NVS vs. HC	Region	LG										IPG							
	H	L										L							
	V	571										1007							
	Coordinates (x, y, z)	−15.23, −33.02, −16.75										−36.99, −42.51, 55.16							
	p	<0.001										<0.001							
VS vs. NVS	Region	MFG											ITG	MOG	CT				
	H	R											R	L	L				
	V	355											462	42,793	496				
	Coordinates (x, y, z)	0.26, 46.49, −28.25											62.49, −49.64, −26.51	−37.46, 85.48, 8.99	−60.74, −53.89, −30.72				
	p	<0.001											<0.001	<0.001	<0.001				

Neutral Emotional Pictures. Hyperactivations *and* Hypoactivations *as reported by Tikàsz et al. (34). H ≙ Hemisphere, V ≙ Cluster Size in Voxels, Coordinates ≙ MNI. MFG ≙ Middle Frontal Gyrus, STG ≙ Superior Temporal Gyrus, SPG ≙ Superior Parietal Gyrus, C ≙ Cuneus, CN ≙ Caudate Nucleus, SFG ≙ Superior Frontal Gyrus, PG ≙ Postcentral Gyrus, LG ≙ Lingual Gyrus, IOG ≙ Inferior Occipital Gyrus, FG ≙ Fusiform Gyrus, IPG ≙ Inferior Parietal Gyrus, ITG ≙ Inferior Temporal Gyrus, MOG ≙ Middle Occipital Gyrus, CT ≙ Cerebellar Tuber.*

TABLE 5D | Activation patterns in emotion induction: auditive emotional words.

Group comparison		Auditive emotional words	
NVS: high vs. low aggression	Region	Hippocampus	Medial Frontal Cortex
	H	L	R
	V	6.078 cm^3	13.251 cm^3
	Coordinates (x, y, z)	−36, −14, 10	31, 52, 18
	p	0.003	0.004

Auditive Emotional Words. Hyperactivations and Hypoactivations as reported by García-Martí et al. (35). H ≙ Hemisphere, V ≙ Cluster Size in Voxels, Coordinates ≙ MNI.

TABLE 6 | Activation patterns in theory of mind task: reading the mind in the eyes test.

Group comparison		Reading the mind in the eyes	
VS vs. NVS	Region	STS	Ventrolateral PFC
	H	L	L
	V	257	286
	Coordinates (x, y, z)	−34, −70, 28	−36, 42, −4
	p	<0.05	<0.05

Theory of Mind. Hyperactivations and Hypoactivations as reported by Schiffer et al. (36). H ≙ Hemisphere, V ≙ Cluster Size in Voxels, Coordinates ≙ MNI, STS ≙ superior temporal sulcus at temporoparietal junction, PFC ≙ prefrontal cortex.

hypothesized that prefrontal dysfunction results in the loss of intellectual flexibility impairing social skills that are essential for non-aggressive solutions.

A PET study with VS showed that repetitive violent offenders hypoactivated the left anterior inferior temporal cortex, while non-repetitive violent offenders hypoactivated this region bilaterally (29). A similar population showed generalized hypometabolism. The authors conclude that anterior temporal structures may control aggression (30).

DISCUSSION

We found non-systematic functional correlates of aggression in schizophrenia. Despite the clinical importance of the topic, only a limited number of studies could be included in this first systematic review on functional neuroimaging correlates of aggression in persons with psychotic disorders. No original research data was available on persons with affective psychoses. Considering the 12 studies in patients with schizophrenia-spectrum disorders (SSD) that could be included, there was considerable sample overlap, and functional neuroimaging paradigms covered a broad range of tasks. While this enables a better overview over which mechanisms could play a role for aggression in SSD, it complicates an integration of the individual findings into a common framework and impedes a quantitative synthesis of the published results. Furthermore, all of the reported findings have yet to be successfully replicated or refuted.

Working Memory

Working memory is known to be impaired in patients with schizophrenia and there have been reports that limited working memory capacity and functioning are predictive of a more impulsive decision-making style (39). In the following, we report functional magnetic resonance imaging correlates of working memory associated with aggressive as opposed to non-aggressive persons with schizophrenia.

Go/No-Go

Joyal et al. (31) compared go/no-go activation in VS with HC and found hypoactivations in the right middle frontal gyrus, right posterior cingulate gyrus, and right superior temporal gyrus but hyperactivations in the left middle temporal gyrus, right midbrain, right primary somatomotor area, and left parahippocampal gyrus. These results match with the hypothesis by Naudts and Hodgins (17), that VS might suffer from neural dysfunction affecting basal or orbital parts of the prefrontal cortex.

VS vs. HC hypoactivated the left thalamus and left caudate nucleus (26). The finding of decreased thalamus activation does not concord with a previous study where Manoach et al. (40) found that schizophrenia patients activated the thalamus during working memory, while HC did not.

NVS vs. HC hypoactivated the left caudate nucleus (26), a region crucial to executive functioning and working memory deficits in schizophrenia (41, 42). Caudate nucleus hypoactivation in VS vs. HC might therefore not be specific for aggression but rather for schizophrenia itself.

N-Back

Kumari et al. (27) found that VS vs. HC showed hyperactivations in the frontal lobe bilaterally, in the right precuneus and in the right inferior parietal lobe. When comparing NVS with HC, the authors observed hyperactivations in the right precuneus. These findings do not match with a previous study where patients with schizophrenia as opposed to HC showed hyperactivation of the dorsolateral prefrontal cortex, the inferior parietal cortex, and the anterior cingulate (43). Also, schizophrenia patients have been shown to hypoactivate their dorsolateral PFC and hyperactivate their ventrolateral PFC (44).

Furthermore, Kumari et al. (27) reported reduced right inferior parietal activity in the VS group compared to the NVS group and a strong negative association between right inferior parietal activity and the ratings of violence in both groups.

The frontal deficit in VS was only evident when compared to HC but not vs. NVS. These results might suggest non-significant hypoactivation in the frontal regions in NVS vs. HC. A deficit in the inferior parietal region affects executive functioning in schizophrenia and might be associated with violence (45). Furthermore, various studies show that a frontal dysfunction may be associated with violence (46).

Synthesis of Findings From Studies Using Working Memory Paradigms

In **Figure 2**, we provide an overview on working memory activation patterns over all reviewed studies. As shown in

Figure 2A, violent as opposed to non-violent persons with schizophrenia showed hypoactivation in the right inferior parietal lobe. This is an area known for being part of the working memory network, but it has until now not been observed in specific aggression paradigms. The hypoactivation seen in this group comparison may therefore not be specific for aggression, but may represent working memory dysfunction in the VS group.

Figure 2B shows hyperactivations of VS as compared to HC mainly in the frontal lobe and in the middle temporal gyrus. In addition, we see hypoactivations of VS as opposed to HC in the right middle frontal gyrus, the cingulate gyrus, and in the superior temporal gyrus. As frontal regions are typically involved in working memory tasks, this finding is in line with the literature.

In **Figure 2C**, we present the activation patterns of NVS as compared to HC. NVS hyperactivate the left caudate nucleus and precuneus. The precuneus is known to be involved in working memory processes, while the caudate nucleus usually is not. Still, the latter—as a feedback processor—might be under higher workload conditions while solving these tasks in persons with schizophrenia than in healthy controls. Also, this could be an indicator toward the hypothesis that schizophrenia patients solve working memory tasks differently, namely trying to use information from past experiences to influence their decisions in the tasks.

Face Affect Recognition

Individuals with schizophrenia suffer from difficulties in recognizing emotional states (47). Persons with antisocial behavior also tend to show deficits in recognizing facial emotion expression with the amygdala being specifically involved in the processing of fearful facial affect (48). In the following, we will in detail disentangle the results of studies on face affect recognition in persons suffering from schizophrenia with vs. without aggression.

VS with high psychopathy scores hyperactivated right amygdala when viewing and identifying disgustful faces, but hypoactivated it when viewing and identifying fearful faces (32). HC activate their left inferior frontal gyrus when viewing fearful faces (49). A meta-analysis by Fusar-Poli et al. (50) integrated findings stating that healthy controls activated the amygdala when viewing happy, fearful, and sad faces. Angry and disgusted faces activated the insula (50).

Persons with schizophrenia react to emotional stimuli by exhibiting reduced activation in the amygdala but increased activation in other regions that are usually not associated with emotion (51). Literature reporting brain activation to facial expressions in psychopathic samples is sparse. However, Deeley et al. (52) examined brain function as individuals with psychopathy and healthy controls processed facial emotion. When viewing happy faces, both groups hyperactivated the fusiform and extrastriate cortices, but this increase was significantly smaller in the psychopathy group. When processing fearful faces, healthy controls hyperactivated their fusiform gyrus while the psychopathy group hypoactivated it (52). These findings are not in line with the reviewed findings by Dolan and Fullam (32)—due to many influencing factors like e.g., mere effect of disease, level of psychopathy, and others it is very difficult to interpret these differential activation patterns. One study reported no neural dysfunction in response to angry faces in children with conduct disorder (53). There are no reports of impairments in the recognition of anger in psychopathic samples (48) or in patients with schizophrenia and high psychopathy scores (54). One study reported reduced arousal ratings in response to angry faces in psychopathic women (55). Neural responses are modulated by anxiety (56) and psychopathic traits are associated with low anxiety levels (57). High psychopathy scorers exhibited increased amygdala response to disgustful faces. There are no published studies on disgust in psychopaths but there are reports that individual differences in disgust sensitivity moderate neural responses to disgust stimuli in HC (58, 59).

Synthesis of Findings From Studies Using Face Affect Recognition Paradigms

In **Figure 3**, we provide an overview on activation patterns during face affect recognition over all reviewed studies. In **Figure 3A**, VS show hyperactivation in the right amygdala in persons with high as opposed to low psychopathy scores when viewing facial expressions of disgust. To our knowledge, there are no previous studies on brain activation patterns of aggressive persons on disgustful faces, but it has been observed that more aggressive persons exhibit higher amygdala activation when seeing angry faces (15).

When viewing fearful faces, as shown in **Figure 3B**, VS with high vs. low psychopathy hypoactivated the right amgydala. This is in line with findings reporting that persons with schizophrenia show hypoactivations of the amygdala in response to emotional stimuli.

Emotion Induction

Shock Anticipation

Kumari et al. (28) found that when anticipating electric shock, violent persons with schizophrenia as opposed to HC show hyperactivations in right fusiform/inferior temporal gyrus as well as in right lingual/posterior cingulate gyrus.

When comparing violent with non-violent persons with schizophrenia under shock anticipation, violent persons with schizophrenia hyperactivated their medial prefrontal/cingulate gyrus bilaterally, middle temporal gyrus bilaterally, right posterior cingulate/cuneus, and left middle occipital gyrus.

Concluding, the AC, medial/inferior frontal regions, insula, striatum, and temporal regions were activated during anticipatory fear. These results are in line with a previous study by Chua et al. (60). The cingulate cortex and the insula are activated during emotional recall/imagery (61), while the neural representation of fear has been hypothesized to be located in the AC/medial prefrontal cortex (62).

Negative Emotional Pictures

Tikàsz et al. (34) compared violent schizophrenia with HC and observed significant hyperactivations as response to negative emotional pictures in the right fusiform gyrus, right superior frontal gyrus, right anterior cingulate, left lingual gyrus, and left precentral gyrus.

When comparing non-violent persons with schizophrenia with HC, non-violent persons with schizophrenia showed significantly higher activation in superior temporal gyrus bilaterally, left cerebellum, left posterior cingulate gyrus, left hippocampus, and left inferior parietal lobe. A previous meta-analysis had found no differences in amygdala activations between HC and persons with schizophrenia when exposed to aversive emotional stimuli (63).

Violent as opposed to non-violent persons with schizophrenia showed hyperactivations in response to negative emotional pictures in the right anterior cingulate, right lingual gyrus, left precentral gyrus, right middle frontal gyrus, right inferior frontal gyrus and superior temporal gyrus, globus pallidus bilaterally, right precuneus, and right mid-cingulate.

Tikàsz et al. (34) discussed the increase of the anterior cingulate reactivity to negative stimuli in the violent schizophrenia group as the most important finding. Some authors suggest that the anterior cingulate is crucial for the integration of negative affect and cognitive control (64–66). It is also associated with the generation and regulation of emotion (67) and, due to connections of the anterior cingulate with both the amygdala and the orbitofrontal cortex, the anterior cingulate seems to be critically involved in violent behavior (68). Tikàsz et al. (34) conclude that anterior cingulate dysfunctions are associated with negative stimuli processing in violent persons with schizophrenia and reason that negative emotions may be a factor in preceding violent behavior.

Positive and Neutral Emotional Pictures

Previous literature concerning healthy persons has shown that visual stimuli generally activate the occipital cortex and the amygdala (61). Furthermore, the medial prefrontal cortex was found to play a role in emotional processing across all categories independently of the emotion. Literature on neutral image processing in schizophrenia is sparse.

Non-violent persons with schizophrenia showed significantly lower activation in the left lingual gyrus than HC when viewing positive pictures.

In the neutral emotional pictures condition, violent persons with schizophrenia compared with HC showed significant hyperactivations in right middle frontal gyrus, right superior temporal gyrus, right superior parietal gyrus, right cuneus, left caudate nucleus, left superior frontal gyrus, left postcentral gyrus, left lingual gyrus, left inferior occipital gyrus, and left fusiform gyrus (34).

Non-violent persons with schizophrenia as opposed to HC showed significant hyperactivation in left inferior parietal gyrus (34). This finding fits into a previous study where Habel et al. (69) showed that persons with schizophrenia elicited hyperactivations in the frontal and cingulate areas and the basal ganglia.

Violent vs. non-violent persons with schizophrenia showed, when viewing neutral pictures, hyperactivations in the right middle frontal gyrus, right inferior temporal gyrus, left middle occipital gyrus, and left cerebellar tuber (34). The authors discuss that it remains unclear how these activation patterns are related to aggressive behavior.

Auditive Emotional Words

Sanjuan et al. (70) used an auditory paradigm to induce emotion presenting schizophrenia patients and HC with neutral and emotional words. The authors used stimuli based on the most frequent words heard by psychotic patients with auditory hallucinations. When measuring activations by means of fMRI, patients as opposed to HC showed hyperactivity in the frontal lobe, temporal cortex, insula, cingulate, and amygdala.

García-Martí et al. (35) found that when hearing emotional words, high vs. low aggression violent persons with schizophrenia exhibited hyperactivation in the left hippocampus as well as in the right medial frontal cortex. The authors assume an association between the scale of aggression and certain brain regions responsible for cognitive and emotional processing. They hypothesize the alteration of neuronal circuits to favor a loss of empathic processes which could lead to aggressive behavior. These findings are partly in line with a study by Sanjuan et al. (70) where the authors found hyperactivity in the frontal lobe, temporal cortex, insula, cingulate, and amygdala when schizophrenia patients suffering from auditory hallucinations were confronted with emotional words. It remains unclear to which extent the findings by García-Martí et al. (35) are specific for violent behavior in schizophrenia.

Synthesis of Findings From Studies Using Emotion Induction Paradigms

In **Figure 4**, we provide an overview on activation patterns during emotion induction over all reviewed studies. As with the other multislice activation pattern figures, this can be helpful to enable a synthesis of findings across the published studies. However, the emotion induction tasks used in the different studies vary considerably, and therefore this synthesis of the findings may be of limited use and must be interpreted with caution.

Figure 4A shows the group comparison of violent vs. non-violent persons with schizophrenia over all emotion induction tasks. Only hyperactivations in the right middle frontal gyrus, inferior frontal gyrus, medial prefrontal gyrus, anterior cingulate, lingual gyrus, globus pallidus, mid-cingulate, precuneus, cuneus, middle temporal gyrus, inferior temporal gyrus and in the left middle occipital gyrus, and cerebellar tuber were reported in this group comparison.

When comparing VS with HC, as shown in **Figure 4B**, only hyperactivations can be found. Mainly, the right hemisphere is activated (middle frontal gyrus, parahippocampal gyrus, middle occipital gyrus, anterior cingulate gyrus, cuneus, superior parietal gyrus)—hyperactivations are also seen bilaterally in the superior frontal gyrus, lingual gyrus, fusiform gyrus, superior temporal gyrus and in the left precentral gyrus, caudate nucleus, postcentral gyrus, and inferior occipital gyrus. When comparing NVS with HC (**Figure 4C**), there were hyperactivations in the left cerebellum and the left inferior parietal lobe and a hypoactivation in the lingual gyrus.

The activation patterns in **Figure 4C** differ considerably from the ones shown in the group comparison VS vs. HC in **Figure 4B**—we therefore suspect that emotion networks in particular may play an important role in patients with

schizophrenia and aggression when in comparison with NVS. However, further studies with higher methodological quality and replication studies using comparable emotion induction paradigms are needed to test this hypothesis.

When comparing high vs. low aggressive NVS in emotion induction paradigms (**Figure 4D**), authors reported hyperactivation in the right superior frontal gyrus and the left hippocampus. However, it remains unclear whether these activation patterns are specific for aggression.

Affective Theory of Mind

Affective theory of mind (ToM) refers to the ability to understand other's emotions (36) and plays an important role in aggressive behavior. Affective ToM is impaired in individuals with psychopathy—the impaired emotional responsiveness and a lack of empathy seem to be associated with ventromedial prefrontal cortex and OFC dysfunction (71). Also, the right temporoparietal junction and the cingulate cortex as well as the left supplementary motor area may be involved in affective ToM (72). Schizophrenia patients and HC do not seem to differ in brain activity during a social cognition task examining affective ToM (73).

Schiffer et al. (36) found that, when performing an affective ToM task, VS as compared to NVS hypoactivated the left ventrolateral PFC and left superior temporal sulcus at the temporoparietal junction.

Synthesis of Findings From Studies Using Affective Theory of Mind Paradigms

In **Figure 5**, we provide an overview on activation patterns generated by affective theory of mind paradigms. The only study reporting on this area was performed by Schiffer et al. (36). Hyperactivations were present in the left inferior frontal gyrus and the left superior temporal sulcus reported in the group comparison of violent as opposed to non-violent persons with schizophrenia. Here, activation of the inferior frontal gyrus is compatible with a challenge in language comprehension, while the superior temporal sulcus is known to be implicated in social perception and general theory of mind.

Activation Patterns as Described by Other Studies

Hoptman et al. (37) conducted a resting-state fMRI study to examine amygdala/ventral prefrontal cortex connectivity in aggression and schizophrenia. Patients showed significant reductions in functional connectivity between amygdala and ventral prefrontal cortex. Lower functional connectivity was associated with higher levels of the measures *self-rated aggression, life history of aggression,* and *total arrests.* The authors conclude that amygdala and ventral prefrontal cortex functional connectivity is compromised in schizophrenia and that this compromise is associated with aggression—in other words, that reduced functional connectivity between the amygdala and the prefrontal cortex is associated with higher levels of aggression. This effect was robust when correcting for medication dosage or age and was specific to the amygdala. A previous study examining persons with schizophrenia showed reduced connectivity in the prefrontal-cerebellar and the cerebellar-thalamic limbs but enhanced connectivity in the cortico-cerebellar circuit (74). Another study found that aggressive subjects as opposed to HC did not couple amygdala-OFC during reponses to angry faces (15). The role and specificity of this decreased connectivity between amygdala and frontal brain regions remains unclear.

Spalletta et al. (38) assessed the relationship between prefrontal function and aggression in persons with schizophrenia using single photon emission tomography (SPECT). The authors compared aggressive with non-aggressive schizophrenia patients and found no difference in regional cerebral blood flow during rest. During activation with the WCST, aggressive subjects showed significantly reduced right middle and inferior prefrontal activation in comparison to the non-aggressive subjects. The authors hypothesized that prefrontal dysfunction results in the loss of intellectual flexibility impairing social skills that are essential for non-aggressive solutions. They discussed the relationship of prefrontal dysfunction to increased predisposition toward aggression and concluded that reduced prefrontal functioning could result in a loss of inhibition, which plays a role in aggressive behavior. It might be possible that patients with prefrontal dysfunction were more vulnerable to impulsive aggression due to their impaired self-control and inability to modify and inhibit behavior appropriately (38).

Wong et al. (29) conducted a positron emission tomography study in male violent offenders with schizophrenia or schizoaffective disorder and found that repetitive violent offenders showed reduced absorption of FDG at the left anterior inferior temporal cortex, while non-repetitive violent offenders (who had committed only one act of violence) had bilateral reduction of FDG uptake at both left and right anterior inferior temporal cortex. In comparison to HC, the left anterior inferior temporal cortex was significantly less activated in both patient groups. The authors conclude that anterior temporal structures are important in the control of aggression. It remains unclear whether these findings are specific to aggression, as the study has not been replicated. Wong et al. (30), in a similar study using the same cohort, reported generalized hypometabolism and discussed that these findings were non-specific because they might be the effect of mere normal aging independently of clinical circumstances.

Limitations and Recommendations for Future Research

Both the clinical picture of schizophrenia and aggressive behavior are very heterogeneous and vary extensively. This makes examining aggression in schizophrenia-spectrum disorders using functional neuroimaging a challenge, contributes to the shortcomings of the currently published literature on this topic, and limits the explanatory power of the current systematic review. In the following, we therefore outline recommendations for future research.

Methodological Quality

Operationalization of aggression and violence

Confusion and lack of clear definitions of violence and violent behavior add to the difficulty in operationalizing aggression for

study purposes (75). In most of the reviewed articles, history of violence was not specified and both type and scale of the violent acts remain unclear. Future articles should therefore clearly define and quantify the nature and extent of aggressive behavior, and adhere to common standards in the operationalization of aggression (75). The processes driving aggressive behavior remain unclear in the reviewed studies. Violence could be driven by psychotic experience (e.g., as a self-defensive response toward a perceived threat) or arise from a different developmental trajectory like for example psychopathic personality traits. Although some studies reported psychopathy checklist scores, we were unable to control for this influencing factor.

Predictors of violence and aggression

There is a large amount of basic and clinical research on aggression and violence in general, and on aggression and violence in persons with schizophrenia spectrum disorders, with many known predictors of these behaviors (e.g., substance use disorder, psychopathology, intelligence, psychopharmacological medication). The included studies do not sufficiently report information on these predictors. This is especially important, as co-morbid substance use disorder seems to be a very strong predictor of the risk of violence (2, 4). We recommend that future studies improve the clinical characterization of their study population and report on predictors of aggression in order to allow for moderator evaluation.

Sample Overlap, Lack of Replication, and Focus on Existing Paradigms

Due to the small number of available studies and considerable sample overlap, it is not yet possible to calculate effect size analyses or to conduct a meta-analysis. Future fMRI based research on the clinically important topic of aggression in psychotic disorders is therefore highly warranted. In particular, new patients should be included to avoid further sample overlap. In addition, research should focus on replication of previous findings, or at least include replication as an additional aim of study. When exploring novel study protocols and paradigms, research should seek to improve upon and enhance previous publications by focusing on similar areas. For example, focusing on the domains *working memory* and *face affect recognition* would lead to highly enhanced comparability of papers in a reasonable time period, and would allow for a better synthesis of findings.

Transfer of Research on Aggression and Focus on Networks

Currently, research protocols mainly focus on identifying differences on fMRI activation patterns between persons with psychotic disorders with and without aggression in an exploratory way. Although this is a viable approach, it partly neglects knowledge on aggression in healthy persons and persons with other psychiatric illnesses. Therefore, we encourage hypothesis driven research, investigating functional correlates of aggression in healthy participants and identifying functional neuronal networks of aggression. These findings should be followed-up in persons with psychotic disorders to identify common networks and differences.

Neglected Area: Affective Psychoses

Until now, there are no studies reporting fMRI correlates of aggression in persons with affective psychoses, although this group of persons is known to be at an increased risk for aggressive behavior. The disregard for this group of psychotic disorders severely limits the explanatory power of the literature and our understanding of aggression in psychotic disorders. We therefore recommend that future researchers include persons with affective psychoses. Although any research on affective psychosis would be valuable for the scientific community, they should also take into account the above recommendations and provide good operationalization of aggression, clinical characterization, and focus on adding knowledge with respect to existing study protocols and paradigms used in persons with non-affective psychosis.

Conclusions

We found non-systematic functional correlates of aggression in schizophrenia. Only relatively few studies have been conducted, all using varied paradigms and often overlapping samples. Due to small sample sizes and cohort overlaps future research is highly warranted in order to gain more insight into the topic. Furthermore, no research on persons with affective psychoses has been published so far. There have been no noticeable attempts to replicate any of the observed findings in the published literature. Regarding future directions, we recommend that authors adhere to clear definitions of aggression as well as measurements of psychopathology, comorbidities, and medication. This would allow enhanced comparability of studies and moderator analyses. In addition, replication studies are needed, rather than studies focusing on new paradigms. When exploring novel study protocols and paradigms, research should seek to improve upon and enhance previous findings, and should primarily use an hypothesis driven approach, investigating functional network correlates of aggression.

AUTHOR CONTRIBUTIONS

CH and SW designed the study. SW conducted literature search and data extraction, and CH supervised this process and helped reach a decision in ambiguous cases. SW and CH wrote the initial draft of the paper. SW, SB, UL, R-DS, and CH made substantial contributions to data interpretation, revised the manuscript critically for important intellectual content, approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00777/full#supplementary-material

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C Paper Three

In the following, we display the paper: Huber, C. G., Widmayer, S., Smieskova, R., Riecher-Rössler, A., Stieglitz, R.-D. & Borgwardt, S. (2018). Voxel-Based Morphometry Correlates of an Agitated-Aggressive Syndrome in the At-Risk Mental State for Psychosis and First Episode Psychosis. *Scientific Reports, 8*(1), 16516.

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Voxel-Based Morphometry Correlates of an Agitated-Aggressive Syndrome in the At-Risk Mental State for Psychosis and First Episode Psychosis

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There are mixed reports on structural neuroimaging correlates of aggression in schizophrenia with weak evidence due to cohort overlaps and lack of replications. To our knowledge, no study examined volumetric neuroimaging correlates of aggression in early stages of psychosis. An agitated-aggressive syndrome is present in at-risk mental state (ARMS) and in first-episode psychosis (FEP) – it is unclear whether this syndrome is associated with structural brain abnormalities in early stages of psychosis. Using three-dimensional magnetic resonance imaging and a whole brain voxel-based morphometry approach, we examined 56 ARMS patients, 55 FEP patients and 25 healthy controls. We operationalized aggression using the Excited Component of the Brief Psychiatric Rating Scale (BPRS-EC) and dichotomized our patient group by median split into "BPRS-EC high" (n = 49) and "BPRS-EC low" groups (n = 62). The "BPRS-EC high" group had significantly smaller left lingual gyrus volume than HC. This finding was not present in the "BPRS-EC low" group. In addition, grey matter volume in the left lingual gyrus showed a negative linear correlation with BPRS-EC over all subjects ($\rho = -0.318$; $p = 0.0001$) and in the patient group ($\rho = -0.202$; $p = 0.033$). These findings provide first hints on structural brain abnormalities associated with an agitated-aggressive syndrome in ARMS and FEP patients.

In first-episode psychosis, there is a prevalence of violence in 34.5% and a prevalence of serious violence in 16.6% of cases with the duration of untreated psychosis being an important influencing factor[1]. Violence in this patient group poses severe clinical problems and a challenge for patients, relatives and professionals[2]. The Brief Psychiatric Rating Scale-Excited Component (BPRS-EC) and neuropsychological dysfunction have been shown to predict aggression in first-episode psychosis[3]. We showed earlier that an agitated-aggressive syndrome was already present in at-risk mental state (ARMS) for psychosis and first-episode psychosis (FEP)[4]. Also, there is evidence for an agitated-aggressive syndrome in early-onset psychosis[5]. However, it is not clear whether this agitated-aggressive syndrome is associated with structural brain abnormalities in early stages of psychosis.

Independently of correlates with aggression, there are consistent grey matter (GM) reductions both in ARMS and FEP patients when compared to healthy controls (HC)[6]. Fusar-Poli *et al.* reported GM reductions in the temporal, limbic prefrontal cortex in the ARMS group, and in the temporal insular cortex and cerebellum in the FEP group[6]. Psychosis onset was characterized by GM decreases in temporal, anterior cingulate, cerebellar, and insular regions. Furthermore, GM alterations in the temporal regions were directly related to the severity of psychotic symptoms[6].

There are mixed results on structural neuroimaging correlates of aggression in schizophrenia[7–9]. Most studies operationalized aggression as "history of violence", while others used continuous measures of aggression. In general, findings pointed to decreased brain volumes in aggressive versus non-aggressive schizophrenia patients

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(e.g. decreased volumes in cerebellum, prefrontal cortex, premotor cortex, inferior frontal cortex and hippocampus)[10–15], while others reported a volume increase in specific structures (e.g., increased amygdala volumes in violent schizophrenia patients[11]), or no significant differences in brain volumes[16]. A recent overview on structural magnetic resonance imaging correlates of aggression in psychosis can be found in Widmayer *et al.*[17].

More specifically, schizophrenia patients with a history of violence had a significantly reduced whole-brain volume compared to schizophrenia patients without a history of violence[10]. The violent schizophrenia group showed a significantly larger putamen volume than the non-violent group; also, in that group comparison, amygdala volume was found to be reduced – these findings, though, were not sustained when *Positive and Negative Syndrome Scale* (PANSS) general psychopathology score was used as covariate. Subjects with schizophrenia and a history of violence had smaller whole brain, temporal lobe and hippocampus volumes than schizophrenia patients without a history of violence[11]. However, schizophrenia patients with a history of violence had larger amygdala volumes than the schizophrenia patients without a history of violence. When comparing the anterior cingulate volumes of violent with non-violent patients, they did not differ significantly[16]. Aggressive versus non-aggressive schizophrenia patients exhibited reduced cortical thickness in ventromedial prefrontal and lateral sensorimotor cortex especially in the right hemisphere[15]. All papers mentioned in the above paragraph based their examinations on the same patient sample.

Another study reported reduced grey matter volume in whole brain, hippocampus and parahippocampal gyrus in violent as compared to non-violent schizophrenia patients[12]. Also, violent schizophrenia patients had smaller grey matter volumes in the cerebellum than non-violent schizophrenia patients[13].

In two papers, dimensional measures of aggression were used to examine structural correlates of violence in one sample of schizophrenia patients[18,19]. The first found larger grey matter volumes in the left orbitofrontal cortex to be associated with a higher degree of aggression as rated using the PANSS and the *Overt Aggression Scale* (OAS)[18], while the other reported larger caudate volumes in patients with treatment-resistant schizophrenia[19].

Summing up, there are relatively few and partly contradictory reports on neuroimaging correlates of aggression in schizophrenia, while inconsistent operationalization of aggression, extensive cohort overlaps and lack of replication studies complicate the interpretation and synthesis of the findings. Furthermore, to our knowledge, no study has examined neuroimaging correlates of aggression in the early stages of psychosis.

Therefore, we aimed at characterizing regions where grey matter volume (GMV) is associated with an agitated-aggressive syndrome in early psychosis using voxel-based morphometry (VBM). Because an agitated-aggressive syndrome as measured with the BPRS-EC had previously been reported in ARMS and FEP patients, and BPRS-EC has been shown to predict clinical aggression, we chose to operationalize aggression using this instrument. Furthermore, because none of the previous findings on GMV correlates of aggression in psychosis has been successfully replicated so far, we chose an exploratory whole brain magnetic-resonance imaging (MRI) approach. Based on previous literature, we hypothesized that a subgroup of ARMS and FEP patients would present with an agitated-aggressive syndrome, and that this subgroup would show reduced GMV in brain regions associated with aggression.

Results

Demographics and Clinical Group Differences. As presented in Table 1, there were significant gender differences with an overrepresentation of male participants in the ARMS and FEP patient groups. The groups did not differ significantly in age, but the patient groups showed a significantly lower level of education than the healthy controls.

In our clinical measures, patients showed a significantly higher BPRS total score than healthy controls. Also, the "BPRS-EC high" group exhibited a significantly higher BPRS total score than the "BPRS-EC low" group. BPRS-EC was significantly higher in patients than in healthy controls and higher in the "BPRS-EC high" group than in the "BPRS-EC low" group. *Scale for the Assessment of Negative Symptoms* (SANS) total score was significantly higher in patients than in healthy controls, with the "BPRS-EC high" group showing significantly higher scores than the "BPRS-EC low" group. Both patient groups had a significantly lower *Global Assessment of Functioning* (GAF) total score than healthy controls.

Regarding medication, our patient groups did not differ significantly in the intake of antipsychotic medication, but a significantly higher proportion of the "BPRS-EC high" group were under antidepressant pharmacotherapy than of the "BPRS-EC low" group. At the time of scanning, 12 individuals were medicated with low doses of atypical antipsychotic medication (7 in the "BPRS-EC low" and 5 in the "BPRS-EC high" group), while 28 individuals received antidepressants (11 in the "BPRS-EC low" and 17 in the "BPRS-EC high" group).

With respect to substance use, our groups did not differ significantly in consumption of cannabis, but patients smoked significantly more cigarettes and had significantly increased moderate and uncontrolled alcohol intake than healthy controls.

Table 2 shows the correlations of the BPRS-EC and its items with BPRS total score, BPRS total score without items included in the BPRS-EC, and SANS total. There were weak to moderate positive correlations between the BPRS-EC items *hostility*, *tension*, *uncooperativeness* and *excitement* and BPRS total score without BPRS-EC items, and weak correlations of most BPRS-EC items and BPRS-EC score with SANS total score.

In Table 3, we show the correlations between the BPRS-EC items and BPRS-EC score with the other BPRS items. The individual BPRS items not included in the BPRS-EC showed several very weak to weak positive correlations with the BPRS-EC items and total score. Only anxiety (vs. tension and BPRS-EC), grandiosity (vs. BPRS-EC), suspiciousness (vs. tension and BPRS-EC), and unusual thought content (vs. tension and BPRS-EC) showed positive correlations of moderate strength.

Imaging Results. As shown in Fig. 1, the "BPRS-EC high" group had significantly less GMV in the left lingual gyrus as compared to HC. Statistical threshold was $p < 0.05$ after family-wise error (FWE) correction.

	BPRS-EC high (H) (n = 49)			BPRS-EC low (L) (n = 62)			HC (C) (n = 25)	Statistics (H vs. L vs. C)	Post hoc
	ARMS	FEP	Total	ARMS	FEP	Total			
Gender M/F	13/7	24/5	37/12	28/8	16/10	44/18	11/14	$\chi^2(2) = 8.8$ $p = 0.018$	
Mean age (years) mean (SD)	23.8 (4.1)	26.7 (6.9)	25.5 (6.1)	24.7 (6.0)	28.0 (7.9)	26.1 (7.0)	27.7 (4.5)	$F(2,1) = 0.959$ $p = 0.386$	
Years of education mean (SD)	13.8 (2.4)	12.6 (3.2)	13.1 (2.9)	13.4 (3.1)	13.7 (2.6)	13.5 (2.9)	16.0 (3.1)	$F(2,1) = 6.9$ $p = 0.001$	H < C, L < C
BPRS total mean (SD)	43.6 (9.4)	56.9 (11.3)	52.3 (11.5)	35.7 (6.4)	42.3 (11.2)	38.8 (9.5)	24.5 (1.1)	$F(2,1) = 70.4$ $p < 0.001$	H > C, H > L, L > C
BPRS-EC mean (SD)	7.1 (1.6)	8.3 (2.4)	7.8 (2.2)	4.4 (0.5)	4.2 (0.4)	4.3 (0.5)	4.0 (0.0)	$F(2,1) = 113.2$ $p < 0.001$	H > C, H > L
SANS total Mean (SD)	21.7 (17.1)	25.6 (14.4)	24.1 (15.5)	15.2 (10.7)	18.8 (16.3)	16.8 (13.4)	0.0 (0.0)	$F(2,1) = 26.9$ $p < 0.001$	H > C, H > L, L > C
GAF total Mean (SD)	66.9 (10.7)	54.7 (15.1)	59.8 (14.6)	67.8 (12.2)	60.3 (13.8)	64.6 (13.3)	88.4 (4.4)	$F(2,1) = 43.9$ $p < 0.001$	H < C, L < C
Antipsychotics n (%)	0	12 (24.5%)	12 (24.5%)	0	12 (19.4%)	12 (19.4%)	0	$\chi^2(1) = 0.0$ $p = 0.939$	
Antidepressants n (%)	12 (24.5%)	6 (12.3%)	18 (36.7%)	10 (16.1)	4 (6.4)	14 (22.6%)	0	$\chi^2(1) = 5.5$ $p = 0.188$	
Alcohol n No/Mod/Uncon	6/10/3	11/15/3	17/25/6	6/25/5	8/15/3	14/40/8	1/22/2	$\chi^2(4) = 10.6$ $p = 0.032$	
Cannabis currently n (%)	8 (16.3%)	9 (18.4%)	17 (34.7%)	9 (14.5%)	5 (8.1%)	14 (22.6%)	4 (16%)	$\chi^2(2) = 3.8$ $p = 0.152$	
Smoking cig/day mean (SD)	11.9 (9.1)	10.6 (8.7)	11.1 (8.8)	6.9 (9.3)	12.3 (13.3)	9.2 (11.3)	3.1 (6.4)	$F(2,1) = 5.7$ $p = 0.004$	H > C, L > C

Table 1. Demographics and Clinical Group Differences. Bonferroni correction (at $p < 0.05$) was calculated for *post-hoc* analyses in SPSS 25.0. Abbreviations: BPRS-EC high: individuals prone to psychosis with high BPRS Excited Component score defined as BPRS-EC > 5, listed as H in the Statistics and Post hoc column; BPRS-EC low: individuals prone to psychosis with low BPRS Excited Component score defined as BPRS-EC ≤ 5, listed as L in the Statistics and Post hoc column; HC: healthy controls, listed as C in the Statistics and Post hoc column; BPRS total: Brief Psychiatric Rating Scale total score; BPRS-EC: Brief Psychiatric Rating Scale – Excited Component; SANS total: Scale for the Assessment of Negative Symptoms total score; GAF total: Global Assessment of Functioning total score; Alcohol n = number of subjects consuming alcohol; No: no alcohol; Mod: moderate intake of alcohol; Uncon: uncontrolled drinking; Smoking cig/day: amount of cigarettes smoked per day.

		Hostiliy	Tension	Uncooperativeness	Excitement	BPRS-EC
BPRS total	r	0.475**	0.537**	0.395**	0.412**	0.705**
	p	<0.001	<0.001	<0.001	<0.001	<0.001
	N	124	124	124	124	124
BPRS total without BPRS-EC items	r	0.367**	0.501**	0.229**	0.392**	0.591**
	p	<0.001	<0.001	0.007	<0.001	<0.001
	N	136	136	136	136	136
SANS total	r	0.229*	0.238**	0.212**	0.124	0.325**
	p	0.011	0.008	0.008	0.176	<0.001
	N	121	121	121	121	121

Table 2. Correlations of BPRS-EC items and total score with BPRS total score, BPRS total score without BPRS-EC items, and SANS total score. *Note.* **Correlation is significant at $p < 0.01$ (2-tailed). *Correlation is significant at $p < 0.05$ (2-tailed). r: Pearson's correlation; *p*: two-tailed significance level. BPRS total: Brief Psychiatric Rating Scale total score; BPRS-EC: Brief Psychiatric Rating Scale – Excited Component; SANS total: Scale for the Assessment of Negative Symptoms total score.

There were no significant between-group differences regarding the contrasts "BPRS-EC high" >HC, "BPRS-EC high" > "BPRS-EC low", "BPRS-EC high" < "BPRS-EC low", patients > HC, and patients < HC.

To better understand the relationship between the GMV abnormalities and the BPRS-EC we performed correlation analyses. A negative correlation was detected between GMV in the left lingual gyrus and BPRS-EC score (MNI x, y, z = −15, −87, −2; Fig. 1) in all included individuals ($\rho = -0.318$; $p = 0.0001$) and in the patient group (ARMS & FEP; $\rho = -0.202$; $p = 0.033$).

		Hostiliy	Tension	Uncooperativeness	Excitement	BPRS-EC
Somatic concern	r	0.133	0.162	0.130	0.179*	0.215*
	p	0.124	0.059	0.132	0.037	0.012
	N	136	136	136	136	136
Anxiety	r	0.201*	0.523**	0.109	0.346**	0.497**
	p	0.019	<0.001	0.207	<0.001	<0.001
	N	136	136	136	136	136
Depression	r	0.166	0.283**	0.251**	0.098	0.310**
	p	0.054	0.001	0.003	0.256	<0.001
	N	136	136	136	136	136
Suicidality	r	0.274**	0.182*	0.247**	0.207*	0.354**
	p	0.001	0.034	0.004	0.016	<0.001
	N	136	136	136	136	136
Guilt	r	0.203*	0.248**	0.163	0.173*	0.301**
	p	0.018	0.004	0.058	0.044	<0.001
	N	136	136	136	136	136
Elevated mood	r	0.167	0.102	0.250**	0.232**	0.246**
	p	0.052	0.239	0.003	0.006	0.004
	N	136	136	136	136	136
Grandiosity	r	0.275**	0.291**	0.319**	0.307**	0.427**
	p	0.001	0.001	<0.001	<0.001	<0.001
	N	136	136	136	136	136
Suspiciousness	r	0.396**	0.441**	0.090	0.342**	0.558**
	p	<0.001	<0.001	0.299	<0.001	<0.001
	N	136	136	136	136	136
Hallucinations	r	0.230**	0.377**	−0.037	0.244**	0.373**
	p	0.007	<0.001	0.668	0.004	<0.001
	N	136	136	136	136	136
Unusual thought content	r	0.322**	0.406**	0.075	0.395**	0.482**
	p	<0.001	<0.001	0.387	<0.001	<0.001
	N	136	136	136	136	136
Bizarre behavior	r	0.181*	0.337**	0.067	0.208	0.338**
	p	0.035	<0.001	0.440	0.015	<0.001
	N	136	136	136	136	136
Self-neglect	r	0.066	0.261**	0.073	0.047	0.209*
	p	0.448	<0.001	0.397	0.583	0.015
	N	136	136	136	136	136
Disorientation	r	0.025	−0.085	−0.034	−0.040	−0.036
	p	0.776	0.323	0.695	0.642	0.677
	N	136	136	136	136	136
Conceptual disorganization	r	0.224**	0.125	−0.023	0.114	0.223**
	p	0.009	0.146	0.793	0.188	0.009
	N	136	136	136	136	136
Blunted affect	r	0.204*	0.168	0.139	0.221*	0.317**
	p	0.017	0.051	0.106	0.010	<0.001
	N	136	136	136	136	136
Emotional withdrawal	r	0.108	0.202*	0.099	0.011	0.218*
	p	0.210	0.019	0.254	0.898	0.011
	N	136	136	136	136	136
Motor retardation	r	0.126	−0.062	0.123	0.022	0.047
	p	0.142	0.473	0.152	0.795	0.585
	N	136	136	136	136	136
Distractibility	r	0.125	0.225**	0.172*	0.238**	0.249**
	p	0.146	0.009	0.045	0.005	0.004
	N	136	136	136	136	136

Continued

		Hostiliy	Tension	Uncooperativeness	Excitement	BPRS-EC
Motor hyperactivity	r	−0.041	0.237**	−0.037	0.320**	0.167
	p	0.637	0.005	0.667	<0.001	0.051
	N	136	136	136	136	136
Mannerism and posturing	r	0.090	0.253**	0.220*	0.022	0.174*
	p	0.298	0.003	0.010	0.802	0.043
	N	136	136	136	136	136

Table 3. Correlations of BPRS-EC items and total score with the remaining BPRS items. *Note* **Correlation is significant at $p < 0.01$ (2-tailed). *Correlation is significant at $p < 0.05$ (2-tailed). r: Pearson's correlation; *p:* two-tailed significance level. BPRS: Brief Psychiatric Rating Scale; BPRS-EC: Brief Psychiatric Rating Scale – Excited Component.

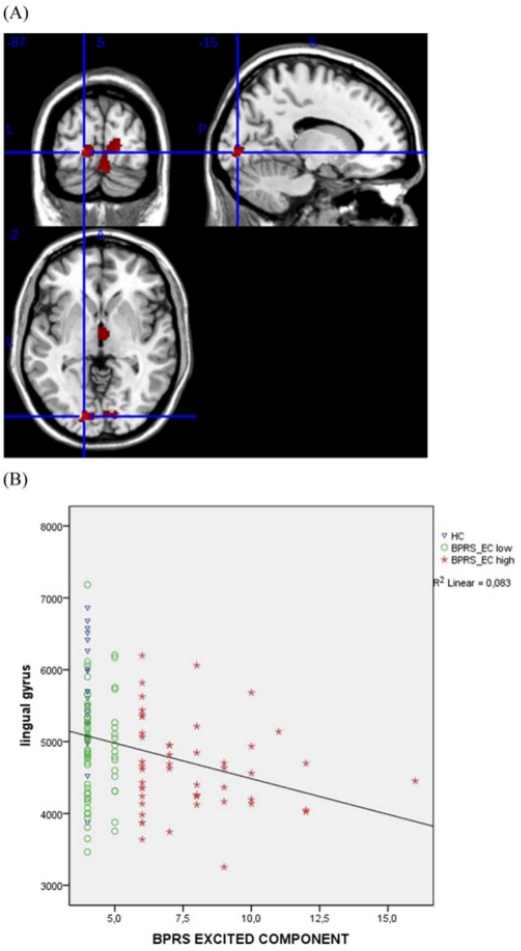

Figure 1. Correlation of BPRS-EC and Lingual Gyrus Volume. Correlation of BPRS-EC and grey matter volume (GMV) in the lingual gyrus. (**A**) The cluster in the lingual gyrus (MNI x, y, z = −15, −87, −2) reflects reduced GMV in the "BPRS-EC high" group compared to the healthy control group [$p < 0.05$ family-wise error (FEW) corrected]. (**B**) Correlation of BPRS-EC and lingual gyrus GMV in this cluster.

Discussion

Aiming at investigating grey matter correlates of aggression, we dichotomized individuals in early stages of psychosis according to BPRS-EC into a "BPRS-EC high" and "BPRS-EC low" group. The BPRS-EC mean value did not differ significantly between the "BPRS-EC low" group and healthy controls.

Our voxel-based morphometry study showed that individuals in early stages of psychosis with an agitated-aggressive syndrome have significant volumetric reductions in the lingual gyrus as opposed to healthy control participants. These volumetric reductions were not evident when comparing BPRS-EC high versus BPRS-EC low groups. This could reflect that a reduced lingual gyrus volume may not exclusively be related to an agitated-aggressive syndrome, but may also in part be a common disease-related correlate of early psychosis – thereby, volumetric alterations could also be present in ARMS and FEP without an agitated-aggressive syndrome to some degree. Furthermore, treatment with antipsychotic medication may already influence potential differences in brain volumes in this early stage of psychosis[20,21]. Longitudinal studies may provide better hints towards an understanding of the specificity of the lingual gyrus volume reduction in aggressive behaviour in schizophrenia.

Lingual gyrus reductions were already described in first-episode psychosis individuals[22,23] – however, the behavioural correlate of this volumetric reduction was unclear. Furthermore, we observed a negative correlation between lingual gyrus volume and BPRS-EC. It has been reported that aggression in psychoses operationalized by dimensional measures (i.e., the PANSS items "Hostility" and "Poor Impulse Control"[24] and the OAS) was associated with larger grey matter volumes in the left orbitofrontal cortex and also larger caudate volumes[18,19]. Our findings might be different because we used an alternative operationalization of aggression. Also, our participants were ARMS and FEP patients compared to the treatment-resistant schizophrenia patients examined by Hoptman *et al.*[18,19]. There are no other studies on structural MRI correlates of aggression in early stages of psychoses. Independently of a psychotic disorder, though, a study examined structural correlates of aggression in patients with borderline personality disorder and found that high as opposed to low lethality suicide attempters had diminished grey matter in an extensive fronto-limbic network including the left lingual gyrus[25]. The authors discuss that deficits in this network could impair social functioning[25]. In studies about correlates of aggression in healthy persons, the lingual gyrus does not seem to be altered.

When looking at functional correlates of aggression in the lingual gyrus, though, we find hints that the region may play an important role. For example, activation to aggressive stimuli in spouse abusers revealed that batterers, relative to controls, showed less activation in the left lingual gyrus when responding to aggressive words[26]. In patients with psychoses, there are two studies reporting functional correlates of aggression in the lingual gyrus. In the first study, participants were threatened to receive an electric shock – when anticipating this shock, violent persons with schizophrenia as opposed to healthy controls showed hyperactivation in the right lingual gyrus[27]. In another study, authors showed negative emotional pictures to their participants and observed that violent persons with schizophrenia as opposed to healthy controls showed significant hyperactivations in the left lingual gyrus[28]. Also, violent as opposed to non-violent persons with schizophrenia showed hyperactivations in response to negative emotional pictures in the right lingual gyrus[28].

The substantial differences in operationalization of aggression and sample composition make studies difficult to compare, and replication studies are needed in order to further evaluate structural correlates of aggression in psychoses.

While there are many results indicating an important role of the lingual gyrus in aggression, it remains unclear exactly how this early volumetric abnormality is associated with aggressive behaviour in early stages of psychoses. Still, our results support the hypothesis that there is, indeed, a structural correlate to an agitated-aggressive syndrome in very early psychoses that is potentially linked to a differential processing of negative emotions.

Some limitations of the current study have to be considered: First, our patient groups differed significantly in the intake of antidepressants and the consumption of nicotine; as we examined an adequate but still small sample, we could not correct for all potential influencing factors in our comparisons. Therefore, we cannot exclude that parts of the reported differences in brain volume may have been affected by substance use. In addition, some potential influencing variables of aggression (e.g., forensic history, antisocial personality disorder) were not available for analysis.

Furthermore, dichotomizing the patient group using a median split may not be an ideal approach, but is a method often used when there is no clear cutoff for clinical relevance, as it is the case with the BPRS-EC. According to the median split, patients with BPRS-EC scores from 4 to 5 were entered in the "BPRS-EC low" subgroup, and patients with BPRS-EC scores from 6 on upwards in the "BPRS-EC high" subgroup. A score of 4 corresponds to complete absence of agitation and aggression (all four items rated as *absent*), and a score of 5 to nearly complete absence with three items rated as *absent*, and one item rated as *very mild*. All control participants in the current study had BPRS-EC scores of 4. Therefore, the median split corresponds to a dichotomization into a group with near complete absence and with the presence of an agitated-aggressive syndrome.

In addition, the "BPRS high" and "BPRS low" subgroups also significantly differed in BPRS and SANS total scores, and it is known that psychopathological symptoms are often interrelated: correlation analyses in our sample showed very weak to moderate correlations between most BPRS-EC items, BPRS items not included in the BPRS-EC, and SANS total score. This raises the question how specific the results are for BPRS-EC. However, the collinearity of BPRS-EC, BPRS total score, and SANS total score also poses a methodological challenge, as controlling for the effect of BPRS total score in our analyses could also diminish or remove true positive findings of significant associations with BPRS-EC. Indeed, exploratory additional VBM analyses in CAT12 (http://www.neuro.uni-jena.de/cat/) including a BPRS sum score without the items present in the BPRS-EC as a covariate did not show significant results any more, but it is unsure how this should be interpreted. In line with the hypothesis presented above, inclusion of the additional BPRS items could lead to a false negative result, and furthermore, the study may be underpowered for this analysis. Concerning the association between BPRS-EC and the SANS,

lingual gyrus volume has until now not been shown to correlate with negative symptoms in schizophrenia[29]. This strengthens the hypothesis that the reduced lingual gyrus volume found in the "BPRS high" group is not associated with increased negative symptoms in this group. Therefore, the presented findings constitute first evidence for a structural correlate of an agitated-aggressive syndrome in ARMS and FEP, but have to be replicated in further studies.

Additionally, the analysis strategy of combining ARMS and FEP patients could be questioned. From the authors' point of view, this decision is warranted because an agitated-aggressive syndrome is already present in ARMS patients[4] and because there is strong evidence supporting a continuum model of psychotic symptoms[30]. However, the theoretical possibility exists that the findings could predominantly be driven by more acutely ill FEP patients and could not be generalizable to ARMS. Again, exploratory additional VBM analyses in CAT12 (http://www.neuro.uni-jena.de/cat/) including a diagnostic group as a covariate did not show significant results any more, but – as noted above – the interpretation of this finding remains unsure with respect to the limited sample size. Although FEP patients showed considerably higher total BPRS total scores than ARMS patients – as has to be expected from the diagnostic and inclusion criteria – this was not the case for BPRS-EC, where the differences between diagnostic groups within the "BPRS-EC high" (7.1 vs. 8.3) and "BPRS-EC low" (4.4 vs. 4.2) groups were small to negligible. In addition, although the percentage of FEP patients in the "BPRS-EC high" group was higher compared to the "BPRS-EC low group" (59.2% vs. 41.9%), this difference also seems small considering the potential systematic effect of the diagnostic criteria. Again, the current study has to be considered a pilot study presenting first evidence for a structural correlate of an agitated-aggressive syndrome in ARMS and FEP, and replication studies are needed.

Lastly, the results would not hold if an initial peak-level threshold of $p < 0.001$ had been chosen. Together with the ongoing discussion about the possible inflation of false positive results due to cluster-level corrections[31] and the controversy on whether or not to use VBM[32] – particularly when examining small samples – this is a further limitation of the current study.

Still, our findings constitute a first hint that the left lingual gyrus GMV may be inversely correlated with an agitated-aggressive syndrome in early stages of psychoses. If this finding could be reliably replicated it may constitute the first step in translational research towards formulation of specific biological hypotheses on the nature of aggressive behaviour in early stages of psychoses and in the prevention of aggressive behaviour in schizophrenia.

Materials and Methods

Study Sample. The current analyses are based on data from the early detection of psychosis project (FePsy) at the Department of Psychiatry, University of Basel, Switzerland[4,33,34]. ARMS patients, FEP patients, and HC for the current analyses were included from November 2008 to April 2014. We identified the patient groups using the criteria of Yung *et al.*[35] – a detailed description of the study design can be found in Riecher-Rössler *et al.*[33].

The inclusion criteria for the ARMS group (n = 56) were one or more of the following: (a) "attenuated" psychotic symptoms; (b) brief limited intermittent psychotic symptoms; (c) a first-degree relative with a psychotic disorder plus a marked decline in social or occupational functioning; or (d) unspecific risk category[33,34,36]. Risk assessment was performed with the Basel Screening Instrument for Psychosis (BSIP) specifically designed for early stages of psychosis[37]. After the baseline assessment, the ARMS subjects were followed up clinically and received standard psychiatric case management. 13 out of 56 included ARMS individuals made the transition to psychosis (23% transition rate).

FEP patients (n = 55) fulfilled criteria for acute psychotic disorder according to the ICD-10 or DSM-IV. Brief Psychiatric Rating Scale (BPRS) ratings were conducted by trained raters during the clinical interviews, and all information available (chart reviews, and third-party accounts where applicable) was used in the assessment. Inclusion required $\geq$4 on the *hallucination* item or $\geq$5 on the *unusual thought content*, *suspiciousness* or *conceptual disorganization* items of the BPRS[35], with symptoms occurring at least several times a week and persisting for more than one week. These inclusion criteria predominantly identify patients with a first episode of schizophrenia (F20.x), delusional disorder (F22.x), acute and transient psychotic disorder (F23.x), schizoaffective disorder (F25.x), and other (F28.x) and unspecified (F29.x) nonorganic psychotic disorder[33].

As an agitated-aggressive syndrome is already present in ARMS and FEP patients[4], we chose not to perform separate analyses for FEP and ARMS patients, but to examine them as one patient group. For the analysis related to the agitated-aggressive syndrome we dichotomised this patient group according to BPRS-EC using a median split ($\text{median}_{\text{BPRS-EC}} = 5$). We then labelled patients with a BPRS-EC score >5 as the "BPRS-EC high" (n = 49) subgroup and patients with a BPRS-EC score $\leq$5 as the "BPRS-EC low" (n = 62) subgroup.

We recruited healthy volunteers (HC, n = 25) from the same geographical area as the clinical groups. The healthy controls had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, substance abuse and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical assessment. Data are available on request.

We applied the following exclusion criteria to our patient groups: history of previous psychotic disorder; psychotic symptomatology secondary to an 'organic' disorder; recent substance abuse (exception: cannabis) according to ICD-10 research criteria; psychotic symptomatology associated with an affective psychosis or a borderline personality disorder; age <18 years; inadequate knowledge of the German language; and IQ <70 as measured with the multiple choice word test (MWT-B)[38].

The study was approved by the local research ethics committee of the University of Basel, *Ethikkommission Nordwest- und Zentralschweiz EKNZ*, and all participants provided written informed consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Clinical Assessment Scales. The Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Excited Component (PANSS-EC) has been identified as a stable factor in patients with schizophrenia spectrum disorders, but item composition may differ depending on the examined study population[2]. The original PANSS-EC proposed by Lindenmayer *et al.*[39] consisted of the items *uncooperativeness*, *poor impulse control*, *excitement*, and *hostility*, and did not include the item *tension* due to moderate factor loading[39]. However, PANSS-EC subscales comprising the five items *poor impulse control*, *tension*, *hostility*, *uncooperativeness*, and *excitement* have also been repeatedly identified[2]. In analogy, BPRS-EC subscales have been constructed encompassing the items *excitement*, *hostility*, and *uncooperativeness* with[4] or without the item *tension*[5]. In the current study, to ensure comparability with previous studies in patients with ARMS and recent onset psychosis, we assessed subjects using the BPRS-EC containing the items *excitement*, *hostility*, *uncooperativeness* and *tension*[3]. Also, subjects were assessed with the SANS[40] and GAF[41] at the time of scanning. Additionally, we obtained current and previous alcohol, nicotine, cannabis and other illegal drug consumption using a semi-structured interview adapted from the Early Psychosis Prevention and Intervention Centre (EPPIC) Drug and Alcohol Assessment Schedule (http://www.eppic.org.au).

Structural Magnetic Resonance Image Acquisition. We acquired a three-dimensional T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence on a 3-T MRI system (Magnetom Verio, Siemens Healthcare, Germany) with sagittal orientation based on a $256 \times 256 \times 176$ matrix, with 1 mm isotropic spatial resolution, inversion time (TI) of 1000 ms, repetition time (TR) of 2 s and echo time (TE) of 3.4 ms. An experienced neuroradiologist screened the scans for gross radiological abnormalities.

Image Analysis. We used SPM8 software (http://www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, UK) running under Matlab 7.1 (MathWorks, USA) to identify group-related differences in grey matter volume (GMV). Voxel-based morphometry was performed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/; earlier VBM analyses with the sample are reported in Smieskova, Borgwardt *et al.*[30,42,43]). T1-weighted MPRAGE images were co-registered to the Montreal Neurological Institute (MNI) template using a multiple stage affine transformation with 12 estimated parameters of interest. These normalized images were segmented using the New Segmentation approach with different treatment of the mixing proportions. Afterwards the changes in volume induced by normalization were corrected using the DARTEL toolbox to produce a high-dimensional normalization protocol[31]. We smoothed all preprocessed images using an isotropic 8 mm Gaussian kernel. We then identified five subjects with a mean covariance below two standard deviations and screened their volumes thoroughly: We found no artefacts and an adequate quality of images. We therefore decided to continue the statistical analysis with all included subjects.

We performed an analysis of covariance (ANCOVA) to compare grey matter images between our three groups ("BPRS-EC high", "BPRS-EC low" and HC) in the whole brain using voxel based morphometry. We modelled age, gender and total intracranial volume (ICV) as covariates of no interest to reduce the potential impact of these variables on the findings. Statistical significance was assessed at cluster level at a threshold of $p < 0.005$, uncorrected (cluster-forming threshold) and inferences were made at $p < 0.05$ after family-wise error (FWE) correction. The eigenvariates from between-group contrasts were extracted and used for correlation analyses between grey matter volume by agitated-aggressive syndrome score.

Statistical Analyses of Demographics and Clinical Group Differences. We performed ANOVAs and χ^2-tests to describe group characteristics with regard to gender, age, years of education, BPRS total score and BPRS-EC, SANS total score, GAF score, intake of antipsychotics and antidepressants, as well as consumption of alcohol, cannabis and cigarettes. ANOVAs were followed-up using post-hoc Bonferroni analyses to identify subgroup differences. Furthermore, we calculated Pearson's correlations for BPRS-EC items and BPRS-EC with BPRS total score, SANS total score, and the BPRS items not included in the BPRS-EC. Correlation strength was assessed as very weak ($r < 0.200$), weak ($0.200 \leq r < 0.400$), moderate ($0.400 \leq r < 0.600$), strong ($0.600 \leq r < 0.800$), and very strong ($r \geq 0.800$) as recommended by Evans (1996)[44]. All analyses were performed with the "Statistical Package for Social Sciences" (IBM SPSS Statistics 25.0), and $p < 0.05$ was considered as significant.

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Author Contributions

A.R.R., R.D.S. and S.B. designed the study. R.S. and S.B. collected the data. R.S., S.W., L.E., C.G.H. and S.B. analyzed and interpreted the data. R.S., C.G.H. and S.W. wrote the initial draft of the manuscript and R.S. prepared the figure and tables. R.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. All authors have contributed to, read and approved the final version of the manuscript.

Additional Information

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